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(54) Title: SUCCINOYLAMINO HYDROXYETHYLAMINO SULFAMIC ACID DERIVATIVES USEFUL AS RETROVIRAL PROTEASE INHIBITORS

(57) Abstract

Succinoylamino hydroxyethylamino sulfamic acid derivative compounds are effective as retroviral protease inhibitors, and in particular as inhibitors of HIV protease.

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SUCCINOYLAMINO HYDROXYETHYLAMINO SULFAMIC ACID DERIVATIVES USEFUL AS RETROVIRAL PROTEASE INHIBITORS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to retroviral protease inhibitors and, more particularly, relates to novel compounds and a composition and method for inhibiting retroviral proteases. This invention, in particular, relates to sulfamic acid-containing hydroxyethylamine protease inhibitor compounds, a composition and method for inhibiting retroviral proteases such as human immunodeficiency virus (HIV) protease and for treating a retroviral infection, e.g., an HIV infection. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

2. Related Art

During the replication cycle of retroviruses, gag and gag-pol gene products are translated as proteins. These proteins are subsequently processed by a virally encoded protease (or proteinase) to yield viral enzymes and structural proteins of the virus core. Most commonly, the gag precursor proteins are processed into the core proteins and the pol precursor proteins are processed into the viral enzymes, e.g., reverse transcriptase and retroviral protease. It has been shown that correct processing of the precursor proteins by the retroviral protease is necessary for assembly of infectious virons. For example, it has been shown that frameshift mutations in the protease region of the pol gene of HIV prevents processing of the gag precursor protein. It has also been shown through site-directed mutagenesis of an aspartic acid residue in the HIV

protease that processing of the gag precursor protein is prevented. Thus, attempts have been made to inhibit viral replication by inhibiting the action of retroviral proteases.

Retroviral protease inhibition may involve a transition-state mimetic whereby the retroviral protease is exposed to a mimetic compound which binds to the enzyme in competition with the gag and gag-pol proteins to thereby inhibit replication of structural proteins and, more importantly, the retroviral protease itself. In this manner, retroviral replication proteases can be effectively inhibited.

Several classes of compounds have been proposed, particularly for inhibition of proteases, such as for inhibition of HIV protease. Such compounds include hydroxyethylamine isosteres and reduced amide isosteres. See, for example, EP O 346 847; EP O 342,541; Roberts et al, "Rational Design of Peptide-Based Proteinase Inhibitors, "Science, 248, 358 (1990); and Erickson et al, "Design Activity, and 2.8Å Crystal Structure of a C_2 Symmetric Inhibitor Complexed to HIV-1 Protease," Science, 249, 527 (1990).

Several classes of compounds are known to be useful as inhibitors of the proteolytic enzyme renin. See, for example, U.S. No. 4,599,198; U.K. 2,184,730; G.B. 2,209,752; EP O 264 795; G.B. 2,200,115 and U.S. SIR H725. Of these, G.B. 2,200,115, GB 2,209,752. EP O 264,795, U.S. SIR H725 and U.S. 4,599,198 disclose urea-containing hydroxyethylamine renin inhibitors. G.B. 2,200,115 also discloses sulfamic acid-containing hydroxyethylamine renin inhibitors, and EP 0264 795 discloses certain sulfamic acid-containing

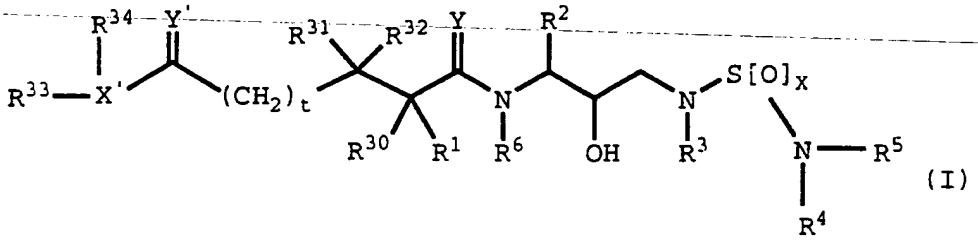
hydroxyethylamine renin inhibitors. However, it is known that, although renin and HIV proteases are both classified as aspartyl proteases, compounds which are effective renin inhibitors generally cannot be predicted to be effective HIV protease inhibitors.

BRIEF DESCRIPTION OF THE INVENTION

The present invention is directed to virus inhibiting compounds and compositions. More particularly, the present invention is directed to retroviral protease inhibiting compounds and compositions, to a method of inhibiting retroviral proteases, to processes for preparing the compounds and to intermediates useful in such processes. The subject compounds are characterized as sulfamic acid-containing hydroxyethylamine inhibitor compounds.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a retroviral protease inhibiting compound of the formula:



(I)

or a pharmaceutically acceptable salt, prodrug or ester thereof wherein:

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine methionine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, O-alkyl serine, aspartic acid, beta-cyanoalanine and valine side chains;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radials, $-NO_2$, $-CN$, $-CF_3$, $-OR^9$ and $-SR^9$, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone and sulfoxide derivatives thereof;

R^4 and R^5 independently represent hydrogen and radicals as defined by R^3 or together with a nitrogen atom to

which they are bonded form a heterocycloalkyl or a heteroaryl radical;

R^6 represents hydrogen and alkyl radicals;

R^{30}, R^{31} and R^{32} independently represent radicals as defined for R^1, or one of R^1 and R^{30} together with one of R^{31} and R^{32} and the carbon atoms to which they are attached form a cycloalkyl radical;

R^{33} and R^{34} independently represent hydrogen and radicals as defined for R^3, or R^{33} and R^{34} together with X' represent cycloalkyl, aryl, heterocyclyl and heteroaryl radicals, provided that when X' is O, R^{34} is absent;

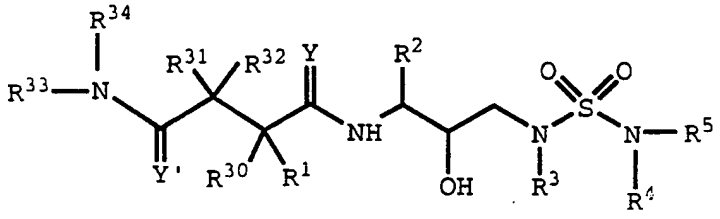
x represents 1 or 2;

X' represents N, O and $C(R^{17})$ wherein R^{17} represents hydrogen and alkyl radicals;

t represents either 0, 1 or 2; and

Y and Y' independently represent O, S and NR^{15} wherein R^{15} represents hydrogen and radicals as defined for R^3.

A family of compounds of particular interest within Formula I are compounds embraced by Formula II:



(II)

wherein:

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine, methionine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, O-methyl serine, aspartic acid, beta-cyanoalanine and valine side chains;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, $-NO_2$, $-C\equiv N$, CF_3, $-OR^9$, $-SR^9$, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone and sulfoxide derivatives thereof;

R^4 and R^5 independently represent hydrogen and radicals as defined by R^3, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and heteroaryl radicals;

R^{30}, R^{31} and R^{32} independently represent radicals as defined for R^1, or one of R^1 and R^{30} together with one of R^{31} and R^{32} and the carbon atoms to which they are attached form a cycloalkyl radical;

R^{33} and R^{34} independently represent hydrogen and radicals as defined for R^3, or R^{33} and R^{34} together with the nitrogen atom to which they are attached represent heterocycloalkyl and heteroaryl radicals; and

Y and Y' independently represent O, S and NR^{15} wherein R^{15} represents hydrogen and radicals as defined for R^3.

A more preferred family of compounds within Formula II consists of compounds wherein:

R^1 represents hydrogen and $CH_2C(O)NHCH_3$, $C(CH_3)_2(SCH_3)$, $C(CH_3)_2(S[O]CH_3)$, $C(CH_3)_2(S[O]_2CH_3)$, alkyl, alkenyl and alkynyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, tert-leucine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine;

R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula $-OR^9$ and $-SR^9$ wherein R^9 represents alkyl radicals; and

R^3 represents alkyl, haloalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals;

R^4 and R^5 independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals, or R^4 and R^5 together with the nitrogen atom to which they are bonded form a heterocycloalkyl or heteroaryl radical;

R^{30}, R^{31} and R^{32} independently represent hydrogen and alkyl, alkenyl and alkynyl radicals, or one of R^1 and R^{30} together with one of R^{31} and R^{32} and the carbon atoms to which they are attached form a cycloalkyl radical;

R^{33} and R^{34} independently represent hydrogen and alkyl, alkenyl and alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals; and

Y and Y' represent O.

Of highest interest are compounds within Formula II wherein

R^1 represents hydrogen and $CH_2C(O)NHCH_3$, $C(CH_3)_2(SCH_3)$, $C(CH_3)_2(S[O]CH_3)$, $C(CH_3)_2(S[O]_2CH_3)$, methyl, ethyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, methionine, allo-iso-leucine, iso-leucine, and beta-cyano alanine side chains;

R^2 represents $CH_3SCH_2CH_2$-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals;

R^3 represents propyl, isoamyl, n-butyl, isobutyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals;

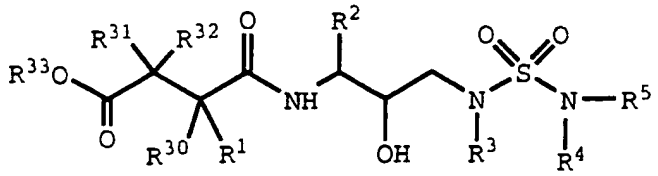
R^4 and R^5 independently represent hydrogen and methyl, ethyl, i-propyl, propyl, n-butyl, t-butyl, 1,1-dimethylpropyl and phenyl radicals, or together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl or N'-alkylpiperazinyl radical;

R^{30}, R^{31} and R^{32} independently represent hydrogen and methyl, ethyl, propyl, butyl, pentyl and hexyl radicals, or one of R^1 and R^{30} together with one of R^{31} and R^{32} form a cycloalkyl radical having from 3 to 8 carbon atoms;

R^{33} and R^{34} independently represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl and hexyl radicals, cyclohexylmethyl, cyclohexyl, benzyl and naphthylmethyl radicals; and

Y and Y' represent O.

Another family of compounds of particular interest within Formula I are compounds embraced by Formula III:



(III)

wherein:

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine, methionine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, aspartic acid, beta-cyano alanine and valine side chains;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, $-NO_2$, $-C\equiv N$, CF_3, $-OR^9$, $-SR^9$, wherein R^9 represents hydrogen and alkyl;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they

are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone and sulfoxide derivatives thereof;

R^4 and R^5 independently represent hydrogen and radicals as defined for R^3 or together with a nitrogen atom to which they are bonded form a heterocycloalkyl or a heteroaryl radical; and

R^{30}, R^{31} and R^{32} independently represent radicals as defined for R^1, or one of R^1 and R^{30} together with one of R^{31} and R^{32} and the carbon atoms to which they are attached form a cycloalkyl radical;

R^{33} represents hydrogen and radicals as defined for R^3.

A more preferred family of compounds within Formula III consists of compounds wherein

R^1 represents hydrogen, alkyl, alkenyl and alkynyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, tert-leucine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, methionine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine;

R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula $-OR^9$ and $-SR^9$ wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents alkyl, haloalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals;

R^4 and R^5 independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals, or R^4 and R^5 together with the nitrogen atom to which they are bonded from a heterocycloalkyl or heteroaryl radical; and

R^{30}, R^{31} and R^{32} independently represent hydrogen and alkyl, alkenyl and alkynyl radicals, or one of R^1 and R^{30} together with one of R^{31} and R^{32} and the carbon atoms to which they are attached form a cycloalkyl radical;

R^{33} represents hydrogen, alkyl, alkenyl and alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals.

Of highest interest are compounds within Formula III wherein

R^1 represents hydrogen, methyl, ethyl, propargyl, t-butyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, methionine, allo-iso-leucine, iso-leucine, threonine, serine, aspartic acid, beta-cyano alanine, and allo-threonine side chains;

R^2 represents $CH_3SCH_2CH_2$-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals;

R^3 represents propyl, isobutyl, isoamyl, n-butyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals;

R^4 and R^5 independently represent hydrogen and methyl, ethyl, i-propyl, n-butyl, t-butyl, 1,1-dimethylpropyl and phenyl radicals, or R^4 and R^5 together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl radical; and

R^{30}, R^{31} and R^{32} independently represent hydrogen and methyl, ethyl, propyl, butyl, pentyl and hexyl radicals, or one of R^1 and R^{30} together with one of R^{31} and R^{32} form a cycloalkyl radical having from 3 to 8 carbon atoms; and

R^{33} represents hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary-butyl, pentyl and hexyl radicals, cyclohexylmethyl, cyclohexyl, benzyl and naphthylmethyl radicals.

As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to about 10, preferably from 1 to 8, carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like. The term "alkenyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radial having one or more double bonds and containing from 2 to about 18 carbon atoms preferably from 2 to 8 carbon atoms. Examples of suitable alkenyl radicals include ethenyl, propenyl, 1,4-butadienyl, 12-octadecene and the like. The term "alkynyl", alone or

in combination, means a straight-chain hydrocarbon radical having one or more triple bonds and containing from 2 to about 10 carbon atoms, preferably from 2 to 8 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, (propargyl), butynyl and the like. The term "alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like. The term "cycloalkyl", alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from about 3 to about 8 carbon atoms and is cyclic. The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical containing from about 3 to about 8, preferably from 3 to 6 carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The term "aryl", alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, and the like. The term "aralkyl", alone or in combination, means an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, 2-phenylethyl and the like. The term "aralkoxy carbonyl", alone or in combination, means a radical of the formula -C(O)-O-aralkyl in which the term "aralkyl" has the significance given above. An example of an aralkoxycarbonyl radical is benzyloxycarbonyl. The term

"aryloxy" means a radical of the formula aryl-O- in which the term aryl has the significance given above. The term "alkanoyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid wherein alkane means a radical as defined above for alkyl. Examples of alkanoyl radicals include acetyl, propionyl, butyryl, valeryl, 4-methylvaleryl, and the like. The term "cycloalkylcarbonyl" means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropanecarbonyl, cyclohexanecarbonyl, adamantanecarbonyl, and the like, or from a benz-fused monocyclic cycloalkanecarboxylic acid which is optionally substituted by, for example, alkanoylamino, such as 1,2,3,4-tetrahydro-2-naphthoyl,2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl. The term "aralkanoyl" means an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl. 4-aminohydrocinnamoyl,4-methoxyhydrocinnamoyl, and the like. The term "aroyl" means an acyl radical derived from an aromatic carboxylic acid. Examples of such radicals include aromatic carboxylic acids, an optionally substituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like. The heterocyclyl or heterocycloalkyl portion of a heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkoxycarbonyl, or heterocyclylalkyl group or the like is a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle which contains one or more hetero atoms selected from nitrogen,

oxygen and sulphur, which is optionally substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo, and the like, and/or on a secondary nitrogen atom (i.e., -NH-) by alkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom (i.e. = N-) by oxido and which is attached via a carbon atom. The heteroaryl portion of a heteroaroyl, heteroaryloxycarbonyl, or a heteroaralkoxy carbonyl group or the like is an aromatic monocyclic, bicyclic, or tricyclic heterocycle which contains the hetero atoms and is optionally substituted as defined above with respect to the definition of heterocyclyl. Such heterocyclyl and heteroaryl radicals have from four to about 12 ring members, preferably from 4 to 10 ring members. Examples of such heterocyclyl and heteroaryl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol 4-yl, 1-benzyloxycarbonylimidazol-4-yl, etc.), pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, furyl, thienyl, triazolyl, oxazolyl, thiazolyl, indolyl (e.g., 2-indolyl, etc.), quinolinyl, (e.g., 2-quinolinyl, 3-quinolinyl, 1-oxido-2-quinolinyl, etc.), isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, etc.), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydro-2-quinolyl, etc.), 1,2,3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, etc.), quinoxalinyl, ß-carbolinyl, 2-benzofurancarbonyl, 1-,2-,4- or 5-benzimidazolyl, and the like. The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkoxycarboxylic acid of the formula cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the significance given above. The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the significance given above. The term "heterocyclyloxycarbonyl" means an acyl

group derived from heterocyclyl-O-COOH wherein heterocyclyl is as defined above. The term "heterocyclylalkanoyl" is an acyl radical derived from a heterocyclyl-substituted alkane carboxylic acid wherein heterocyclyl has the significance given above. The term "heterocyclylalkoxycarbonyl" means an acyl radical derived from a heterocyclyl-substituted alkane-O-COOH wherein heterocyclyl has the significance given above. The term "heteroaryloxycarbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-O-COOH wherein heteroaryl has the significance given above. The term "aminocarbonyl" alone or in combination, means an amino-substituted carbonyl (carbamoyl) group derived from an amino-substituted carboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, and alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like. The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkanecarboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, and alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like. The term "halogen" means fluorine, chlorine, bromine or iodine. The term "haloalkyl" means an alkyl radical having the significance as defined above wherein one or more hydrogens are replaced with a halogen. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like. The term "leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are

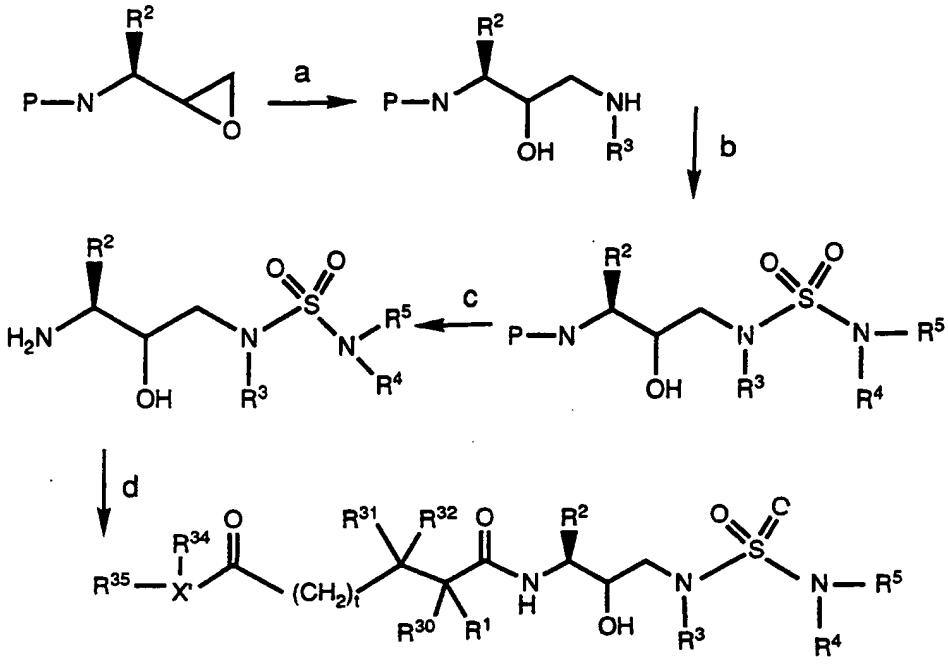
not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

Procedures for preparing the compounds of Formula I are set forth below. It should be noted that the general procedure is shown as it relates to preparation of compounds having the specified stereochemistry, for example, wherein the absolute stereochemistry about the hydroxyl group is designated as (R), which is the preferred stereochemistry for the compounds of the present invention. However, such procedures are generally applicable to those compounds of opposite configuration, e.g., where the stereochemistry about the hydroxyl group is (S). In addition, the compounds having the (R) stereochemistry can be utilized to produce those having the (S) stereochemistry. For example, a compound having the (R) stereochemistry can be inverted to the (S) stereochemistry using well-known methods.

Preparation of Compounds of Formula I

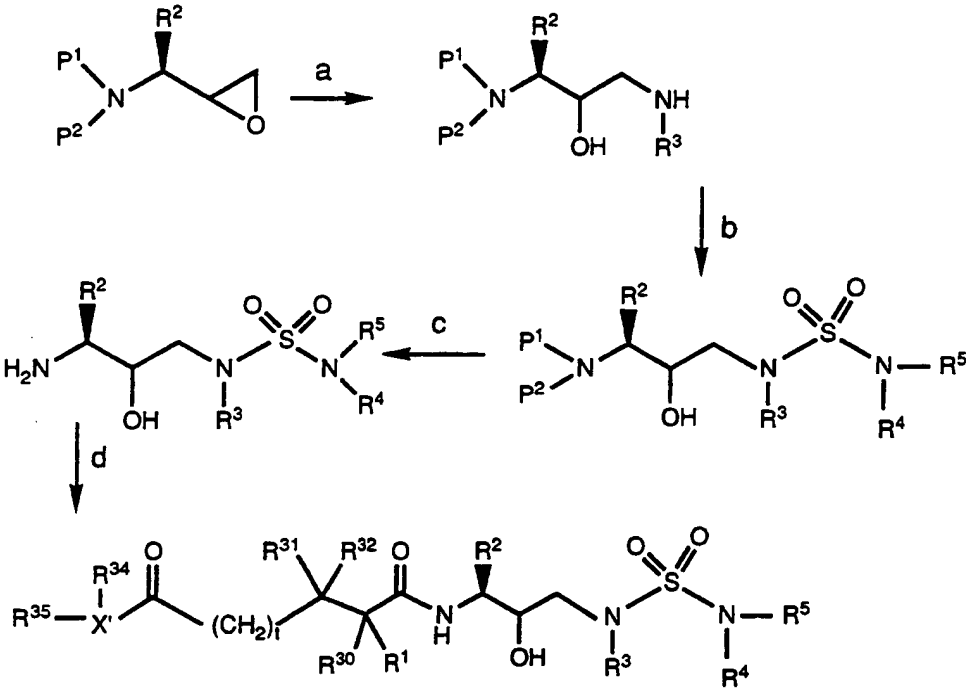
The compounds of the present invention represented by Formula I above can be prepared utilizing the following general procedure. This procedure is schematically shown in the following Schemes I and II:

SCHEME I



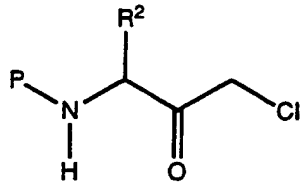
a) amine b) sulfamoyl chloride $R^4R^5NSO_2Cl$ (or anhydride) + acid scavenger c) deprotection d) coupling

SCHEME II



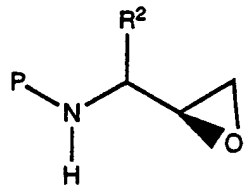
a) amine b) sulfamoyl chloride $R^4R^5NSO_2Cl$ (or annydride) + acid scavenger c) deprotection d) coupling

An N-protected chloroketone derivative of an amino acid having the formula:



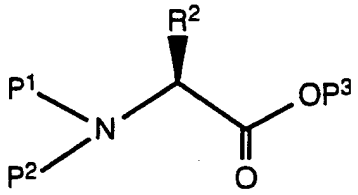
wherein P represents an amino protecting group, and R^2 is as defined above, is reduced to the corresponding alcohol utilizing an appropriate reducing agent. Suitable amino protecting groups are well known in the art and include carbobenzoxy, t-butoxycarbonyl, and the like. A preferred amino protecting group is carbobenzoxy. A preferred N-protected chloroketone is N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone. A preferred reducing agent is sodium borohydride. The reduction reaction is conducted at a temperature of from -10°C to about 25°C, preferably at about 0°C, in a suitable solvent system such as, for example, tetrahydrofuran, and the like. The N-protected chloroketones are commercially available, e.g., such as from Bachem, Inc., Torrance, California. Alternatively, the chloroketones can be prepared by the procedure set forth in S. J. Fittkau, J. Prakt. Chem., 315, 1037 (1973), and subsequently N-protected utilizing procedures which are well known in the art.

The halo alcohol can be utilized directly, as described below, or, preferably, is then reacted, preferably at room temperature, with a suitable base in a suitable solvent system to produce an N-protected amino epoxide of the formula:



wherein P and R^2 are as defined above. Suitable solvent systems for preparing the amino epoxide include ethanol, methanol, isopropanol, tetrahydrofuran, dioxane, and the like including mixtures thereof. Suitable bases for producing the epoxide from the reduced chloroketone include potassium hydroxide, sodium hydroxide, potassium t-butoxide, DBU and the like. A preferred base is potassium hydroxide.

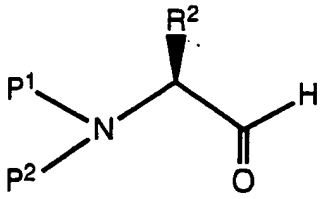
Alternatively, a protected amino epoxide can be prepared starting with an L-amino acid which is reacted with a suitable amino-protecting group in a suitable solvent to produce an amino-protected L-amino acid ester of the formula:



wherein P^1 and P^2 independently represent hydrogen, benzyl and amino-protecting groups (as defined above), provided that P^1 and P^2 are not both hydrogen; P^3 represents carboxyl-protecting group, e.g., methyl, ethyl, benzyl, tertiary-butyl and the like; and R^2 is as defined above.

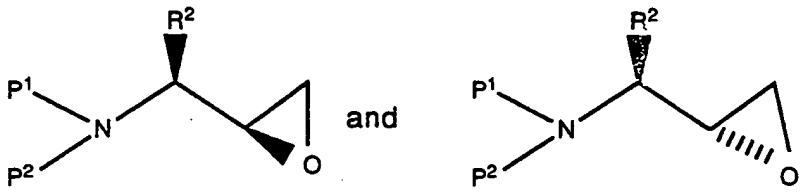
The amino-protected L-amino acid ester is then reduced, to the corresponding alcohol. For example, the

amino-protected L-amino acid ester can be reduced with diisobutylaluminum hydride at -78° C in a suitable solvent such as toluene. The resulting alcohol is then converted, for example, by way of a Swern oxidation, to the corresponding aldehyde of the formula:



wherein P^1, P^2 and R^2 are as defined above. Thus, a dichloromethane solution of the alcohol is added to a cooled (-75 to -68° C) solution of oxalyl chloride in dichloromethane and DMSO in dichloromethane and stirred for 35 minutes.

The aldehyde resulting from the Swern oxidation is then reacted with a halomethyllithium reagent, which reagent is generated <u>in situ</u> by reacting an alkyllithium or arylithium compound with a dihalomethane represented by the formula $X^1CH_2X^2$ wherein X^1 and X^2 independently represent I, Br or Cl. For example, a solution of the aldehyde and chloroiodomethane in THF is cooled to -78° C and a solution of n-butyllithium in hexane is added. The resulting product is a mixture of diastereomers of the corresponding amino-protected epoxides of the formulas:

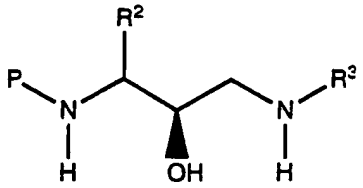
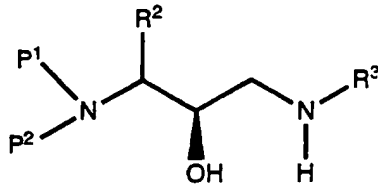


The diastereomers can be separated e.g., by chromatography, or, alternatively, once reacted in subsequent steps the diastereomeric products can be separated. For compounds having the (S) stereochemistry, a D-amino acid can be utilized in place of the L-amino acid.

The amino epoxide is then reacted, in a suitable solvent system, with an equal amount, or preferably an excess of, a desired amine of the formula:

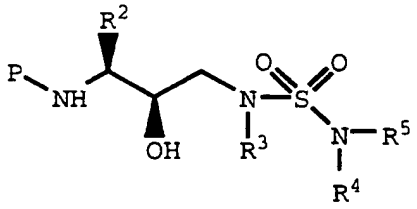
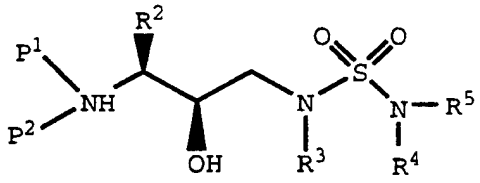
R^3NH_2

wherein R^3 is hydrogen or is as defined above. The reaction can be conducted over a wide range of temperatures, e.g., from about 10°C to about 100°C, but is preferably, but not necessarily, conducted at a temperature at which the solvent begins to reflux. Suitable solvent systems include protic, non-protic and dipolar aprotic organic solvents such as, for example, those wherein the solvent is an alcohol, such as methanol, ethanol, isopropanol, and the like, ethers such as tetrahydrofuran, dioxane and the like, and toluene, N,N-dimethylformamide, dimethyl sulfoxide, and mixtures thereof. A preferred solvent is isopropanol. Exemplary amines corresponding to the formula R^3NH_2 include benzyl-amine, isobutylamine, n-butyl amine, isopentyl amine, isoamylamine, cyclohexanemethyl amine, naphthylene methyl amine and the like. The resulting product is a 3-(N-protected amino)-3-(R^2)-1-(NHR^3)-propan-2-ol derivative (hereinafter referred to as an amino alcohol) can be represented by the formulas:

wherein P, P^1, P^2, R^2 and R^3 are as described above. Alternatively, a haloalcohol can be utilized in place of the amino epoxide.

The amino alcohol defined above is then reacted in a suitable solvent with a sulfamoyl halide, e.g. sulfamoyl chloride ($R^4R^5NSO_2Cl$ or R^4HNSO_2Cl) or sulfamoyl anhydride in the presence of an acid scavenger. Suitable solvents in which the reaction can be conducted include methylene chloride, tetrahydrofuran. Suitable acid scavengers include triethylamine, pyridine. The resulting sulfamic acid derivative can be represented, depending on the epoxide utilized, by the formulas;

wherein P, P^1, P^2, R^2, R^3, R^4 and R^5 are as defined above. These intermediates are useful for preparing inhibitor compounds of the present invention and are also active inhibitors of retroviral proteases.

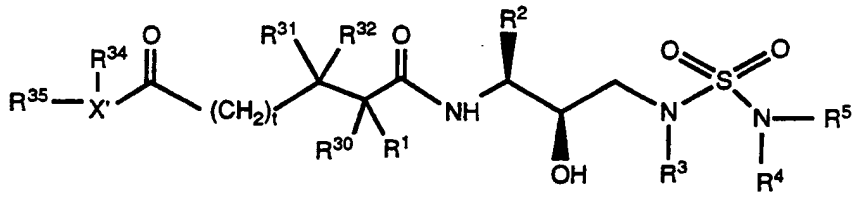
The sulfamoyl halides of the formula R^4NHSO_2X can be prepared by the reaction of a suitable isocyanate of the formula R^4NCO with fuming sulfuric acid to produce the corresponding sulfamate which is then converted to the halide by well known procedures, such as by treating

the sulfamate with PCl_5. Alternatively the isocyanate can be treated with chlorosulfonic acid to produce the corresponding sulfamoyl chloride directly.

The sulfamoyl halides of the formula $R^4R^5NSO_2Cl$ can be prepared by reacting an amine of the formula R^4R^5NH, preferably as a salt such as the hydrochloride, with sulfuryl chloride in a suitable solvent such as acetonitrile. The reaction mixture is gradually warmed to reflux temperature and maintained at the reflux temperature until the reaction is complete. Alternatively, sulfamoyl halides of the formula $R^4R^5NSO_2Cl$ can be prepared by reacting an amine of the fomula R^4R^5NH with sulfuryl chloride in boiling MeCN as disclosed in Matier et al., J. Med. Chem., 15, No. 5, p.538 (1972).

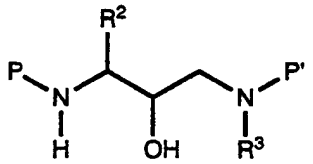
Following preparation of the sulfamic acid derivative, the amino protecting group P or P^1 and P^2 amino protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of the protecting group, e.g., removal of a carbobenzoxy group, by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. Where the protecting group is a t-butoxycarbonyl group, it can be removed utilizing an inorganic or organic acid, e.g. HCl or trifluoroacetic acid, in a suitable solvent system, e.g., dioxane or methylene chloride. Where the protecting group is a benzyl radical, it can be removed by hydrogenolysis. The resulting product is the amine salt derivative. Following neutralization of the salt, the

amine is then reacted with a succinic acid, or derivative thereof, as described below, to produce the antiviral compounds of the present invention having the formula:

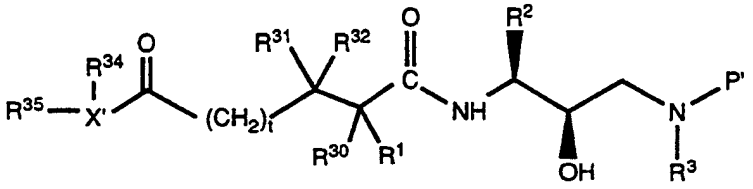


wherein t, R^1, R^2, R^3, R^4, R^5, R^{30}, R^{31}, R^{32}, R^{33} and R^{34} are as defined above.

Alternatively, the protected amino alcohol from the epoxide opening can be further protected at the newly introduced amino group with a protecting group P' which is not removed when the first protecting P is removed. One skilled in the art can choose appropriate combinations of P and P'. One suitable choice is when P is Cbz and P' is Boc. The resulting compound represented by the formula:

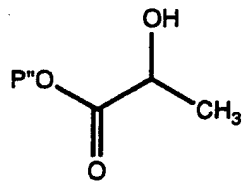


can be carried through the remainder of the synthesis to provide a compound of the formula:

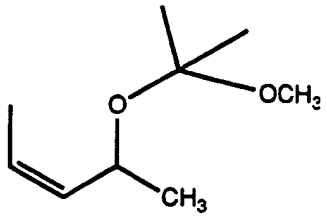


and the new protecting group P' is selectively removed, and following deprotection, the resulting amine reacted to form the sulfamic acid derivative as described above. This selective deprotection and conversion to the sulfamic acid can be accomplished at either the end of the synthesis or at any appropriate intermediate step if desired.

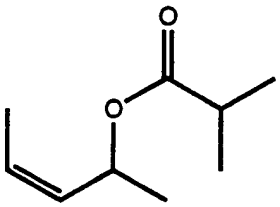
To produce the succinic acid portion of the compounds of Formula I, the starting material is a lactate of the formula:



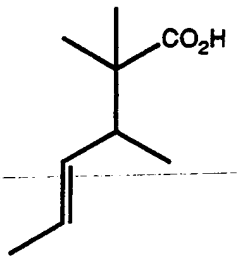
wherein P" represents alkyl and aralkyl radicals, such as, for example, ethyl, methyl, benzyl and the like. The hydroxyl group of the lactate is protected as its ketal by reaction in a suitable solvent system with methyl isopropenyl ether (1,2-methoxypropene) in the presence of a suitable acid. Suitable solvent systems include methylene chloride, tetrahydrofuran and the like as well as mixtures thereof. Suitable acids include $POCl_3$ and the like. It should be noted that well-known groups other than methyl isopropenyl ether can be utilized to form the ketal. The ketal is then reduced with diisobutylaluminum hydride (DIBAL) at -78°C to produce the corresponding aldehyde which is then treated with ethylidene triphenylphosphorane (Wittig reaction) to produce a compound represented by the formula:



The ketal protecting group is then removed utilizing procedures well-known in the art such as by mild acid hydrolysis. The resulting compound is then esterified with isobutyryl chloride to produce a compound of the formula:

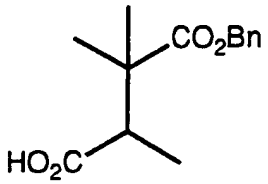


reaction mixture to room temperature to effect a Claisen rearrangement ([3,3]) to produce the corresponding acid represented by the formula:



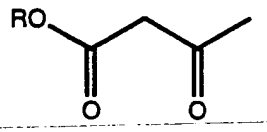
Those skilled in the art will recognize that variations on this scheme are possible, using either different protecting groups or reagents to carry out the same transformations. One can also utilize other acid chlorides in place of isobutyryl chloride to prepare similar analogs.

Treatment of the acid with benzyl bromide in the presence of a tertiary amine base, e.g., DBU, produces the corresponding ester which is then cleaved oxidatively to give a trisubstituted succinic acid:

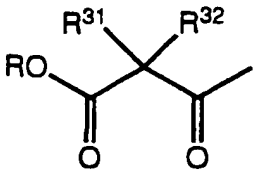


The trisubstituted succinic acid is then coupled to the sulfamate isostere utilizing procedures well known in the art. To produce the free acid, the benzyl ester is removed by hydrogenolysis to produce the corresponding acid. The acid can then be converted to the primary amide by methods well-known in the art. The resulting product is a compound represented by Formula I.

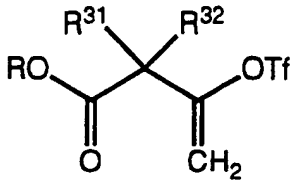
An alternative method for preparing trisubstituted succinic acids involves reacting an ester of acetoacetic acid represented by the formula:



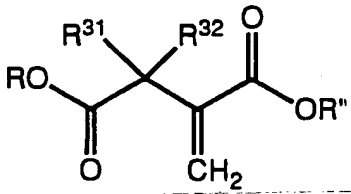
where R is a suitable protecting group, such as methyl, ethyl, benzyl or t-butyl with sodium hydride and a hydrocarbyl halide ($R^{31}X$ or $R^{32}X$) in a suitable solvent, e.g., THF, to produce the corresponding disubstituted derivative represented by the formula:



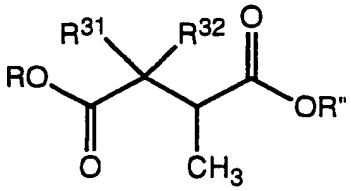
This disubstituted acetoacetic acid derivative is then treated with lithium diisopropyl amide at about -10°C and in the presence of $PhN(triflate)_2$ to produce a vinyl triflate of the formula:



The vinyl triflate is then carbonylated utilizing a palladium catalyst, e.g., $Pd(OAc)_2$ and Ph_3P, in the presence of an alcohol (R"OH) or water (R"=H) and a base, e.g., triethylamine, in a suitable solvent such as DMF, to produce the olefinic ester or acid of the formula:

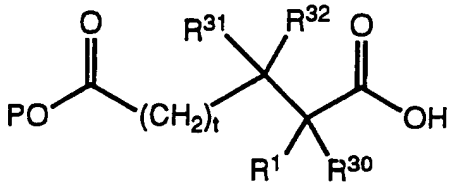


The olefin can then be subsequently asymmetrically hydrogenated, as described below, to produce a trisubstituted succinic acid derivative of the formula:

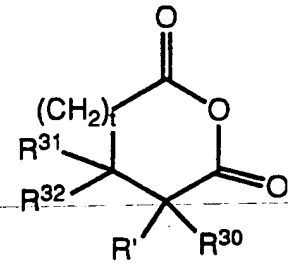


If R" is not H, R" can be removed by either hydrolysis, acidolysis, or hydrogenolysis, to afford the corresponding acid, which is then coupled to the sulfamate isostere as described above and then, optionally, the R group removed to produce the corresponding acid, and optionally, converted to the amide.

Alternatively, one can react the sulfamate isostere with either a suitably monoprotected succinic acid or glutaric acid of the following structure;



followed by removal of the protecting group and conversion of the resulting acid to an amide. One can also react an anhydride of the following structure;



with the sulfamate isostere and then separate any isomers or convert the resulting acid to an amide and then separate any isomers.

It is contemplated that for preparing compounds of the Formulas having R^6, the compounds can be prepared following the procedure set forth above and, prior to

coupling the sulfamate derivative or analog thereof, e.g. coupling to the amino acid $PNH(CH_2)_tCH(R^1)COOH$, carried through a procedure referred to in the art as reductive amination. Thus, a sodium cyanoborohydride and an appropriate aldehyde or ketone can be reacted with the sulfamate derivative compound or appropriate analog at room temperature in order to reductively aminate any of the compounds of Formulas I-IV. It is also contemplated that where R^3 of the amino alcohol intermediate is hydrogen, the inhibitor compounds of the present invention wherein R^3 is alkyl, or other substituents wherein the α-C contains at least one hydrogen, can be prepared through reductive amination of the final product of the reaction between the amino alcohol and the amine or at any other stage of the synthesis for preparing the inhibitor compounds.

Contemplated equivalents of the general formulas set forth above for the antiviral compounds and derivatives as well as the intermediates are compounds otherwise corresponding thereto and having the same general properties, such as tautomers thereof as well as compounds, wherein one or more of the various R groups are simple variations of the substituents as defined therein, e.g., wherein R is a higher alkyl group than that indicated. In addition, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, e.g., a hydrocarbyl radical or a halogen, hydroxy, amino and the like functional group, is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure.

The chemical reactions described above are generally disclosed in terms of their broadest

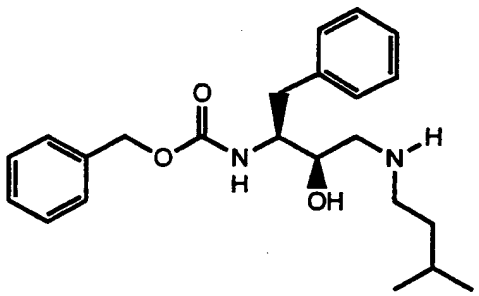
application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

All reagents were used as received without purification. All proton and carbon NMR spectra were obtained on either a Varian VXR-300 or VXR-400 nuclear magnetic resonance spectrometer.

The following Examples 1 through 9 illustrate preparation of intermediates. These intermediates are useful in preparing the inhibitor compounds of the present invention as illustrated in Examples 13-17. In addition, the intermediates of Examples 4-9 are also retroviral protease inhibitors and inhibit, in particular, HIV protease.

Example 1



Preparation of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-isoamylamine

Part A:

To a solution of 75.0g (0.226 mol) of N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone in a mixture of 807 mL of methanol and 807 mL of tetrahydrofuran at -2°C, was added 13.17g (0.348 mol, 1.54 equiv.) of solid sodium borohydride over one hundred minutes. The solvents were removed under reduced pressure at 40°C and the residue dissolved in ethyl acetate (approx. 1L). The solution was washed

sequentially with 1M potassium hydrogen sulfate, saturated sodium bicarbonate and then saturated sodium chloride solutions. After drying over anhydrous magnesium sulfate and filtering, the solution was removed under reduced pressure. To the resulting oil was added hexane (approx. 1L) and the mixture warmed to 60°C with swirling. After cooling to room temperature, the solids were collected and washed with 2L of hexane. The resulting solid was recrystallized from hot ethyl acetate and hexane to afford 32.3g (43% yield) of N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol, mp 150-151°C and $M+Li^+$ = 340.

Part B:

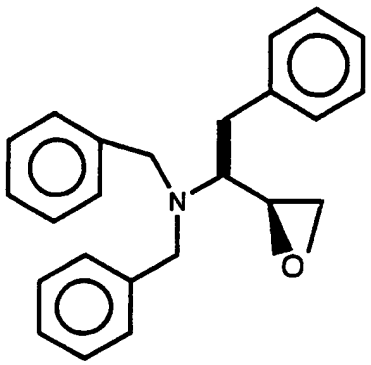
To a solution of 6.52g (0.116 mol, 1.2 equiv.) of potassium hydroxide in 968 mL of absolute ethanol at room temperature, was added 32.3g (0.097 mol) of N-CBZ-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After stirring for fifteen minutes, the solvent was removed under reduced pressure and the solids dissolved in methylene chloride. After washing with water, drying over magnesium sulfate, filtering and stripping, one obtains 27.9g of a white solid. Recrystallization from hot ethyl acetate and hexane afforded 22.3g (77% yield) of N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane, mp 102-103°C and MH^+ 298.

Part C:

A solution of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane (1.00g, 3.36 mmol) and isoamylamine (4.90g, 67.2 mmol, 20 equiv.) in 10 mL of isopropyl alcohol was heated to reflux for 1.5 hours. The solution was cooled to room temperature, concentrated *in vacuo* and then poured into 100 mL of stirring hexane whereupon the product crystallized from solution. The

product was isolated by filtration and air dried to give 1.18g, 95% of N=[[3(S)-phenylmethylcarbamoyl}amino-2(R)-hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine mp 108.0-109.5°C, MH^+ m/z = 371.

Example 2



Preparation of N,N-dibenzyl-3(S)-amino-1,2-(S)-epoxy-4-phenylbutane

Step A:

A solution of L-phenylalanine (50.0 g, 0.302 mol), sodium hydroxide (24.2 g, 0.605 mol) and potassium carbonate (83.6 g, 0.605 mol) in water (500 ml) is heated to 97°C. Benzyl bromide (108.5 ml, 0.912 mol) is then slowly added (addition time ~25 min). The mixture is then stirred at 97°C for 30 minutes. The solution is cooled to room temperature and extracted with toluene (2 x 250 ml). The combined organic layers are then washed with water, brine, dried over magnesium sulfate, filtered and concentrated to give an oil product. The crude product is then used in the next step without purification.

Step B:

The crude benzylated product of the above step is dissolved in toluene (750 ml) and cooled to -55°C. A 1.5 M solution of DIBAL-H in toluene (443.9 ml, 0.666 mol) is then added at a rate to maintain the temperature between -55° to -50°C (addition time - 1 hour). The mixture is stirred for 20 minutes at -55°C. The reaction is quenched at -55°C by the slow addition of methanol (37 ml). The cold solution is then poured into cold (5°C) 1.5 N HCl solution (1.8 L). The precipitated solid (approx. 138 g) is filtered off and washed with toluene. The solid material is suspended in a mixture of toluene (400 ml) and water (100 ml). The mixture is cooled to 5°C, treated with 2.5 N NaOH (186 ml) and then stirred at room temperature until the solid is dissolved. The toluene layer is separated from the aqueous phase and washed with water and brine, dried over magnesium sulfate, filtered and concentrated to a volume of 75 ml (89 g). Ethyl acetate (25 ml) and hexane (25 ml) are then added to the residue upon which the alcohol product begins to crystallize. After 30 min., an additional 50 ml hexane is added to promote further crystallization. The solid is filtered off and washed with 50 ml hexane to give approximately 35 g of material. A second crop of matrial can be isolated by refiltering the mother liquor. The solids are combined and recrystallized from ethyl acetate (20 ml) and hexane (30 ml) to give, in 2 crops, approximately 40 g (40% from L-phenylalanine) of analytically pure alcohol product. The mother liquors are combined and concentrated (34 g). The residue is treated with ethyl acetate and hexane which provides an additional 7 g (~7% yield) of slightly impure solid product. Further optimization in the recovery from the mother liquor is probable.

Step C:

A solution of oxalyl chloride (8.4 ml, 0.096 mol) in dichloromethane (240 ml) is cooled to -74°C. A solution of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml) is then slowly added at a rate to maintain the temperature at -74°C (addition time ~1.25 hr). The mixture is stirred for 5 min. followed by addition of a solution of the alcohol (0.074 mol) in 100 ml of dichloromethane (addition time -20 min., temp. -75°C to -68°C). The solution is stirred at -78°C for 35 minutes. Triethylamine (41.2 ml, 0.295 mol) is then added over 10 min. (temp. -78° to -68°C) upon which the ammonium salt precipitated. The cold mixture is stirred for 30 min. and then water (225 ml) is added. The dichloromethane layer is separated from the aqueous phase and washed with water, brine, dried over magnesium sulfate, filtered and concentrated. The residue is diluted with ethyl acetate and hexane and then filtered to further remove the ammonium salt. The filtrate is concentrated to give the desired aldehyde product. The aldehyde was carried on to the next step without purification.

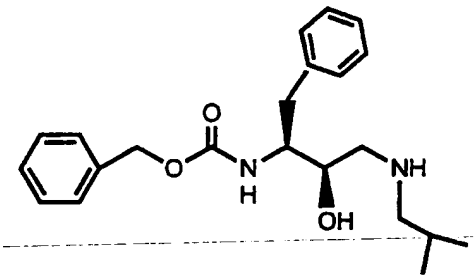
Temperatures higher than -70°C have been reported in the literature for the Swern oxidation. Other Swern modifications and alternatives to the Swern oxidations are also possible.

A solution of the crude aldehyde 0.074 mol and chloroiodomethane (7.0 ml, 0.096 mol) in tetrahydrofuran (285 ml) is cooled to -78°C. A 1.6 M solution of n-butyllithium in hexane (25 ml, 0.040 mol) is then added at a rate to maintain the temperature at -75°C (addition time - 15 min.). After the first addition, additional chloroiodomethane (1.6 ml, 0.022 mol) is added again, followed by n-butyllithium (23 ml, 0.037 mol), keeping

the temperature at -75°C. The mixture is stirred for 15 min. Each of the reagents, chloroiodomethane (0.70 ml, 0.010 mol) and n-butyllithium (5 ml, 0.008 mol) are added 4 more times over 45 min. at -75°C. The cooling bath is then removed and the solution warmed to 22°C over 1.5 hr. The mixture is poured into 300 ml of saturated aq. ammonium chloride solution. The tetrahydrofuran layer is separated. The aqueous phase is extracted with ethyl acetate (1 x 300 ml). The combined organic layers are washed with brine, dried over magnesium sulfate, filtered and concentrated to give a b rown oil (27.4 g). The product could be used in the next step without purification. The desired diastereomer can be purified by recrystallization at a subsequent step.

Alternately, the product could be purified by chromatography.

Example 3

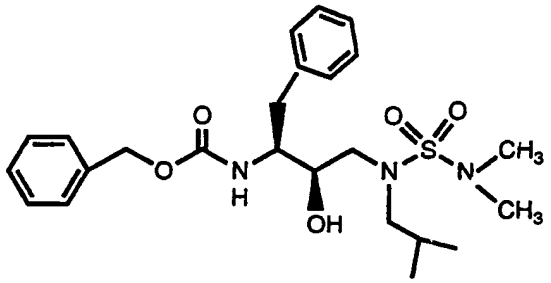


Preparation of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenyl]N-isobutylamine

A solution of N-benzyloxycarbonyl-3(S)-amino-1,2-(S)-epoxy-4-phenyl butane (50.0 g, 0.188 mol) and isobutylamine (246 g, 3.24 mol, 20 equivalents) in 650 mL of isopropyl alcohol was heated to reflux for 1.25 hours.

The solution was cooled to room temperature, concentrated in vacuo and then poured into 1 L of stirring hexane whereupon the product crystallized from solution. The product was isolated by filtration and air dried to give 57.56 g, 92% of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenyl]N-isobutylamine, mp 108.0-109.5 °C, MH+ m/z=371.

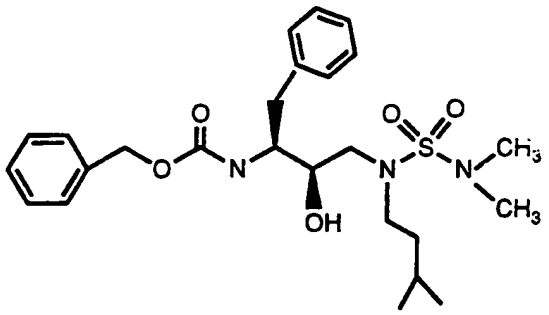
Example 4



Preparation of phenylmethyl[2R-hydroxy-3-[[(dimethylamino)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]carbamate

The product from Example 3 (740 mg, 2.0 mmol) and diisopropylethylamine (382 uL, 2.2 mmol) were dissolved in dichloromethane (1.5 mL) at room temperature. To this was added dimethylsulfamoyl chloride (354 uL, 3.3 mmol). The reaction was stirred for 24 hours. The reaction mixture was chromatographed on silica gel (50 gm) using 1% ethanol in chloroform. The product fractions were pooled and concentrated to an oil. Anal. Calcd for $C_{24}H_{35}N_3O_5S$: C, 60.35; H, 7.39; N, 8.80. Found: C, 60.18; H, 7.40; N, 8.55.

Example 5



Preparation of phenylmethyl[2R-hydroxy-3-[[(dimethylamino)sulfonyl](3-methylbutyl)amino]-1S-(phenylmethyl)propyl]carbamate

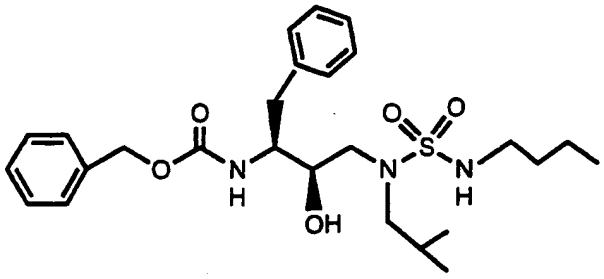
Part A

The procedure described in Example 1 was used to prepare N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-[(3-methylbutyl)]amine.

Part B

The product from Part A (192 mg, 0.5 mmol) and diisopropylethylamine (96 uL, 0.55 mmol) were dissolved in dichloromethane (10 mL) at room temperature. To this was added dimethylsulfamoyl chloride (59 uL, 0.55 mmol). The reaction was stirred for 120 hours, then concentrated on a rotary evaporator. The residue was chromatographed on silica gel (50 gm) using 2% methanol in dichloromethane. The product fractions were pooled and concentrated to an oil which solidified on standing. Anal. Calcd for $C_{25}H_{37}N_3O_5S$. 0.9 H_2O: C, 59.13; H, 7.64; N, 8.27; S, 6.31. Found: C, 58.81; H, 7.38; N, 8.62; S, 6.70.

Example 6



Preparation of phenylmethyl [3-[[(butylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl] carbamate

Part A:

To a stirred solution of 3.88 gm (2 mL) of 30% fuming sulfuric acid in nitromethane (10mL) was added dropwise n-butylisocyanate (3.83 mL, 34 mmoles) at 0 C. After the addition was completed, the suspension was heated in an oil bath at 120 C. for 30 min. The reaction was cooled and filtered. The collected sulfamic acid crystals were air dried, wt. 4.73 gm (91%).

Part B:

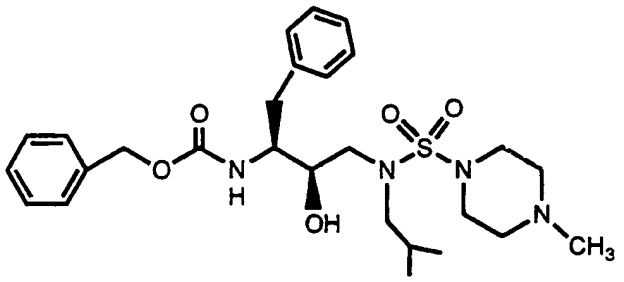
A suspension of n-butyl sulfamic acid (1.92 gm, 12.53 mmoles) and phosphorus pentachloride (2.61 gm, 12.53 mmoles) in benzene (20 mL) was warmed gently to initiate gas evolution. The reaction mixture was stirred at room temperature for 0.5 h., during which time a cloudy solution resulted.The cloudy solution was heated to reflux for 0.5 h., then was concentrated. The product n-butyl sulfamoyl chloride was isolated by vacuum distillation (120 C., 300 millitorr), 730 mg (liq.) (34%).

Part C:

The amino alcohol from Example 3 (370 mg, 1 mmole) was dissolved in 3 mL of dichloromethane and treated with diisopropylethylamine (278 uL, 2 mmoles), followed by chlorotrimethylsilane (126 uL, 1 mmole). The reaction mixture was stirred at r.t. for 1 h. n-Butyl sulfamoyl chloride from Part C (171 mg, 1 mmole) was added and the mixture was stirred at r.t. overnight. After removal of dichloromethane the oily residue was taken up in ethyl acetate and washed successively with 5% citric acid, saturated sodium bicarbonate, brine, dried over sodium sulfate and the solvent was evaporated to give 512 mg of product (oil).

The oily product (510 mg) was dissolved in dichloromethane (3 mL) and was treated with 2 mL of 4N HCl in dioxane. After 15 min. methanol (5 mL) was added and the solution was stirred for an additional 15 min. Solvent and excess reagent were evaporated. The product was isolated by silica gel chromatography to give 357 mg of phenylmethyl [3-[[(butylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl] carbamate. Anal. Calcd for $C_{26}H_{39}N_3O_5S$: C, 61.76; H,7.77; N,8.31. Found: C, 61.89; H,7.66; N, 8.18.

Example 7



Preparation of phenylmethyl [2R-hydroxy-3-[[(4-methyl-1-piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate

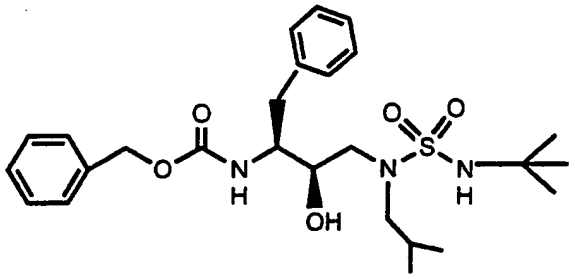
Part A:

1-methylpiperazine hydrochloride (3.46 gm, 20 mmoles) was added in portions within 15 min. to a stirred solution of sulfuryl chloride (8.99 gm, 67 mmoles) in acetonitrile(40 mL). The suspension was gradually warmed to reflux and maintained at reflux temperature overnight. A brown solution was obtained. After cooling to r.t., the crystals were collected by filtration, wt. 2.3 gm. A sample of 4-methyl-1-piperazine sulfamoyl chloride.HCl was recrystallized from methanol. Anal. Calcd. for $C_5H_{12}N_2O_2Cl_2S$: C, 25.54; H, 5.14; N, 11.91; Cl, 30.16. Found: C, 25.54; H, 4.91; N, 11.91; Cl, 29.88.

Part B:

N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine (370 mg, 1.0 mmole), prepared according to the procedure in Example 3 was mixed with DIEA (280 uL, 2.0 mmoles) and 4-methyl-1-piperazine sulfamoyl chloride.HCl (240 mg, 1.0 mmole) in 6 mL of dichloromethane. The reaction mixture was stirred for 5 days. After filtration, the filtrate was concentrated to an oil, which was taken up in ethyl acetate. The ethyl acetate solution was washed with sodium bicarbonate solution, brine and dried over sodium sulfate. After evaporation, phenylmethyl [2R-hydroxy-3-[[(4-methyl-1-piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate was obtained (412 mg).

Example 8



Preparation of phenylmethyl [2R-hydroxy-3-[[(1,1-dimethyl)amino]sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate

Part A:

A 25 mL two-necked RB flask, equipped with a reflux condenser and dropping funnel and under a nitrogen atmosphere, was charged with t-butanol (207 uL, 2.2 mmoles) and 5 mL of hexane. Chlorosulfonyl isocyanate (192 uL, 2.2 mmoles) in 3 mL of hexane was added dropwise. Upon warming a homogeneous solution was obtained. The solution was heated at gentle reflux for 45 min., then was cooled to r.t. Solvent was removed under a steady stream of nitrogen. The crude t-butyl sulfamoyl chloride (a liquid) was used without further purification.

Part B:

N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine (370 mg, 1.0 mmole), prepared according to the procedure in Example 3 was mixed with DIEA (139 uL, 1 mmole) in 5 mL of dichloromethane. Chlorotrimethylsilane (126 uL, 1 mmole) was added. After 1

h., additional DIEA (160 uL) was added, followed by a dichloromethane solution (5mL) containing 1.1 mmole of t-butyl sulfamoyl chloride from Part A. The reaction mixture was stirred for 2 days. Solvent was removed under aspirator pressure. The oily residue was taken up in ethyl acetate and washed with 5% citric acid, saturated sodium bicarbonate, brine, dried over sodium sulfate and evaporated to an oily residue (380 mg).

The crude product was stirred in 4N HCl in dioxane (6 mL) for 15 min. After the addition of 4 mL of methanol to the reaction mixture, the solution was stirred for an additional 15 min, then concentrated to an oily residue. The product, phenylmethyl [2R-hydroxy -3-[[(1,1-dimethylethyl)amino]sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate was obtained after silica gel chromatography (188 mg, 37%). MS (MH)+ = 506.

Part C:

The carbobenzyloxy protecting group of the product from Part B was removed by hydrogenolysis. Thus 1.3 grams of the product of Part B in 50 mL of methanol was hydrogenated under 50 psig of hydrogen using 0.7 g of 10% palladium-on-carbon catalyst 18 hours. The catalyst was removed by filtration and the solvent removed in vacuo to afford 0.75 g of the free amine.

Example 9

Phenylmethyl [2R-hydroxy-3-[[(piperidyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]carbamate

Part A:

The product of Example 3 (750 mg, 2.02 mmol) and triethylamine (280 uL, 2.02 mmol) were dissolved in dichloromethane (8.0 mL) at room temperature. To this was added piperidinesulfamoyl chloride (371 mg, 2.02 mmol). The reaction was stirred for 72 hours and then concentrated. The residue was chromatographed on silica gel (50 gm) using 5% methanol in dichloromethane. The product fractions were pooled and concentrated to an oil, 945 mg. TLC (silica / 5% MeOH in CH2Cl2) showed two spots. Rechromatographed. Anal. Calcd for C27H39N3O5S: C, 62.63; H, 7.51; N, 8.06. Found: C, 62.64; H, 7.59; N, 8.12.

Part B:

The product of Part A (430 mg) was combined with 10% Pd/C in methanol (10 mL) and hydrogenated at 5 psi for 1.4 hours at room temperature. The catalyst was removed by filtration and the solvent evaporated to afford the product as an oil, 305 mg.

Part C:

To a solution of Cbz-L-t-leucine (236 mg, 0.89 mmol) in DMF (2 mL) was added HOBt (115 mg, 0.85 mmol) and EDC (163 mg, 0.85 mmol). The reaction was stirred at room temperature for 1 hour and then a solution of the product from part B (305 mg, 0.79 mmol) in DMF (2 mL) was added. The reaction was stirred for 18 hours then concentrated. The residue was taken up in ethyl acetate and washed with 0.5% HCl solution, saturated aqueous NaHCO3 , and saturated aqueous NaCl (50 mL each). The organic solution was dried (Na2SO4), filtered and concentrated to a foam, 410 mg. 1H NMR supports product.

Part D:

The product of Part C (410 mg) was combined with 10% Pd/C in methanol (10 mL) and hydrogenated at 5 psi for 2.0 hours

at room temperature. The catalyst was removed by filtration and the solvent evaporated to afford the product as an foam, 320 mg.

Part E:

To a solution of the product of Part D (310 mg, 0.62 mmol) in dichloromethane (10 mL) was added diisopropylethylamine (130 uL, 0.75 mmol) and chloroacetic anhydride (117 mg, 0.68 mmol) at 0 C. The reaction was allowed to warm to room temperature and stir one hour. The solvent was removed and the residue taken up in ethyl acetate (50 mL). The organic solution was washed with 5% citric acid, saturated NaHCO3, and saturated NaCl (50 mL each). The solution was dried (Na2SO4) , filtered and concentrated to give a solid, 350 mg.

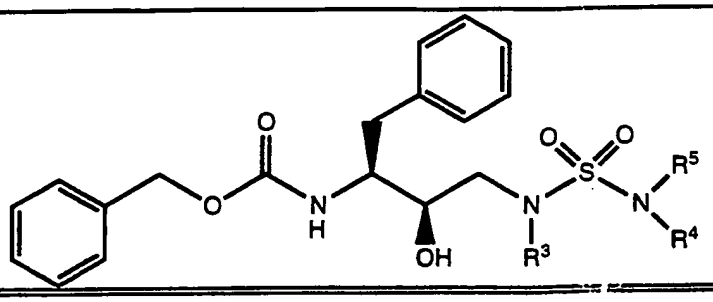
Part F:

The product of Part E (350 mg, 0.61 mmol) was combined with 40% aqueous dimethylamine (380 uL, 3.05 mmol) in isopropanol (10 mL). The reaction was stirred for 18 hours then concentrated. The residue was taken up in ethyl acetate (50 mL) and washed with water, saturated NaHCO3, and saturated NaCl (50 mL each). The solution was dried (Na2SO4) , filtered and concentrated to a solid. The solid was chromatographed on silica gel using 2% MeOH in dichloromethane. The product fractions were pooled and concentrated to give a white solid. Anal. Calcd for C29H51N5O5S. 0.25 H2O: C, 59.41; H, 8.77; N, 11.94. Found: C, 59.35; H, 8.78; N, 11.63.

Example 10

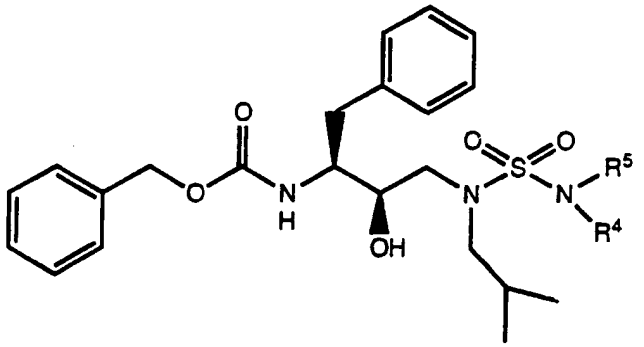
Following the procedures of the previous Examples 1-9, the intermediate compounds set forth in Tables 1A, 1B and 1C were prepared.

TABLE 1A



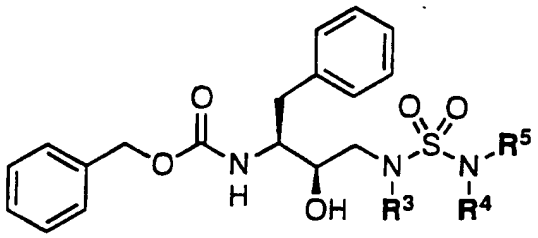
R^3	R^4	R^5
isobutyl	CH_3	CH_3
isoamyl	CH_3	CH_3
isobutyl	$CH_2CH_2CH_2CH_3$	H

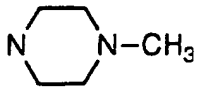
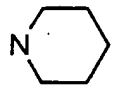
TABLE 1B



Entry	R^4	R^5
1	CH_3	CH_3
2	H	CH_3
3	H	$(CH_2)_3CH_3$
4	H	$CH(CH_3)_2$
5	H	$C(CH_3)_3$
6	H	C6H5
7	H	C6H11
8		

Table 1C

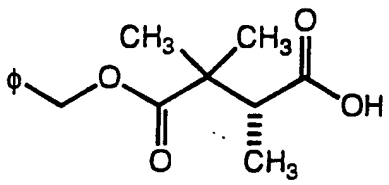


Entry	R^3	R^4	R^5
A	isobutyl	methyl	H
B	p-fluorobenzyl	methyl	methyl
C	isobutyl	isopropyl	H
D	isobutyl	NR^4R^5 = 	
E	isobutyl	phenyl	H
F	isobutyl	NR^4R^5 = 	
G	isobutyl	NR^4R^5 = 	
H	benzyl	t-butyl	H
I	cyclohexylmethyl	t-butyl	H
J	isobutyl	$C(CH_3)_2CO_2Me$	H
K	cyclohexyl	t-butyl	H
L	$(CH_2)_2OCH_2C_6H_5$	isobutyl H	
M	isobutyl	cyclohexyl	H

The following Examples 11-14 illustrate preparation of succinoyl compounds. These intermediates can be coupled to the intermediate compounds of Examples

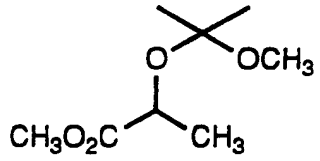
1-10 to produce inhibitor compounds of the present invention.

Example 11



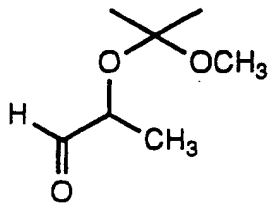
Preparation of Benzyl 2,2,3(R)-trimethylsuccinate

PART A: Preparation of Methyl (S)-lactate, 2-methoxy-2-propyl ether.



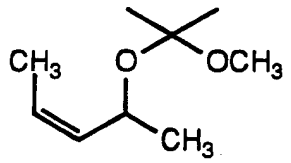
To a mixture of methyl(S)-(-)-lactate (13.2g, 100 mmol) and, 2-methoxypropene (21.6g, 300 mmol) in CH_2Cl_2 (150 ml) was added $POCl_3$ (7 drops) at r.t. and the resulting mixture was stirred at this temperature for 16 hours. After the addition of Et_3N (10 drops), the solvents were removed in vacuo to give 20.0g of (98%) desired product.

PART B: Preparation of 2(S)-hydroxypropanal, 2-methoxy-2-propyl ether.



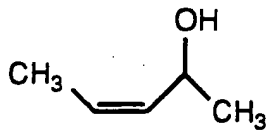
To a solution of compound from Part A (20.0g) in CH_2Cl_2 (100 ml) was added DIBAL (65 ml of 1.5M solution in toluene, 97.5 mmol) dropwise at -78°C for 45 min., then stirring was continued at this temperature for another 45 min. To this cold solution was added MeOH (20 ml), saturated NaCl solution (10 ml) and allowed the reaction mixture to warm up to r.t. and diluted with ether (200 ml), $MgSO_4$ (150g) was added and stirred for another 2 h. The mixture was filtered and the solid was washed twice with ether. The combined filtrates were rotavaped to afford 11.2g (78%) of the desired aldehyde.

PART C: Preparation of 2(S)-hydroxy-cis-3-butene, 2-methoxy-2-propyl ether.



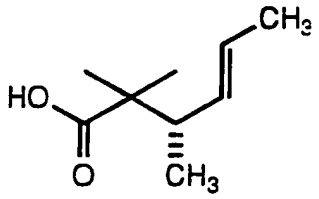
To a suspension of ethyltriphenylphosphonium bromide (28g, 75.5 mmol) in THF (125 ml) was added KN $(TMS)_2$ (15.7g, 95%, 75 mmol) in portions at 0°C and stirred for 1 h at the temperature. This red reaction mixture was cooled to -78°C and to this was added a solution of aldehyde from Part B (11g, 75 mmol) in THF (25 ml). After the addition was completed, the resulting reaction mixture was allowed to warm up to r.t. and stirred for 16 h. To this mixture was added saturated NH_4Cl (7.5 ml) and filtered through a pad of celite with a thin layer of silica gel on the top. The solid was washed twice with ether. The combined filtrates were concentrated in vacuo to afford 11.5g of crude product. The purification of crude product by flash chromatography (silica gel, 10:1 Hexanes/EtoAc) affording 8.2g (69%) pure alkene.

PART D: Preparation of 2(S)-hydroxy-cis-3-butene.



A mixture of alkene from Part C (8.2g) and 30% aqueous acetic acid (25 ml) was stirred at r.t. for 1 hour. To this mixture was added $NaHCO_3$ slowly until the pH was ~ 7, then extracted with ether (10 ml x 5). The combined ether solutions were dried (Na_2SO_4) and filtered. The filtrate was distilled to remove the ether to give 2.85g (64%) pure alcohol, m/e=87(M+H).

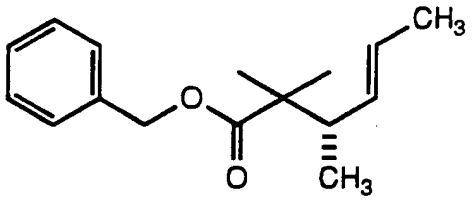
PART E: Preparation of 2,2,3-trimethyl-hex-(trans)-4-enoic acid.



To a mixture of alcohol from Part D (2.5g, 29 mmol) and pyridine (2.5 ml) in CH_2Cl_2 (60 ml) was added isobutyryl chloride (3.1g, 29 mmol) slowly at 0°C. The resulting mixture was stirred at r.t. for 2 hours then washed with H_2O (30 ml x 2) and sat. NaCl (25 ml). The combined organic phases were dried (Na_2SO_4), concentrated to afford 4.2g (93%) ester 2(S)-hydroxy-cis-3-butenyl isobutyrate. This ester was dissolved in THF (10 ml) and was added to a 1.0M LDA soln. (13.5 ml of 2.0M LDA solution in THF and 13.5 ml of THF) slowly at -78°C. The resulting mixture was allowed to warm up to r.t. and stirred for 2 h and diluted with 5% NaOH

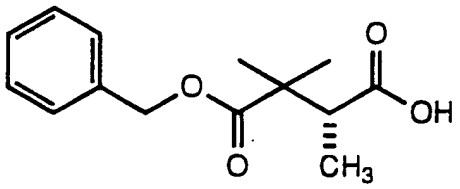
(40 ml). The organic phase was separated, the aqueous phase was washed with Et_2O (10 ml). The aqueous solution was collected and acidified with 6N HCl to pH ~ 3. The mixture was extracted with ether (30 ml x 3). The combined ether layers were washed with sat. NaCl (25 ml), dried (Na_2SO_4) and concentrated to afford 2.5g (60%) of desired acid, m/e=157(M+H).

PART F: Preparation of benzyl 2,2,3(S)-trimethyl-trans-4-hexenoate.



A mixture of acid from Part E (2.5g, 16 mmol), BnBr (2.7g, 15.8 mmol), K_2CO_3 (2.2g, 16 mmol), NaI (2.4g) in acetone (20 ml) was heated at 75°C (oil bath) for 16 h. The acetone was stripped off and the residue was dissolved in H_2O (25 ml) and ether (35 ml). The ether layer was separated, dried (Na_2SO_4) and concentrated to afford 3.7g (95%) of benzyl ester, m/e=247(M+H).

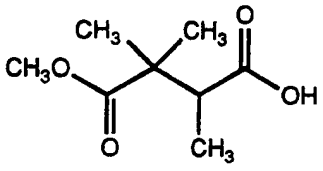
PART G: Preparation of benzyl 2,2,3(R)-trimethylsuccinate.



To a well-stirred mixture of $KMnO_4$ (5.4g, 34, 2 mmol), H_2O (34 ml), CH_2Cl_2 (6 ml) and benzyltriethylammonium chloride (200 mg) was added a

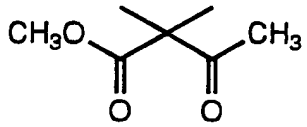
solution of ester from Part F (2.1g, 8.54 mmol) and acetic acid (6 ml) in CH_2Cl_2 (28 ml) slowly at 0°C. The resulting mixture was stirred at the temperature for 2 h then r.t. for 16 h. The mixture was cooled in an ice-water bath, to this was added 6N HCl (3 ml) and solid $NaHSO_3$ in portions until the red color disappeared. The clear solution was extracted with CH_2Cl_2 (30 ml x 3). The combined extracts were washed with sat. NaCl solution, dried (Na_2SO_4) and concentrated to give an oil. This oil was dissolved in Et_2O (50 ml) and to this was added sat. $NaHCO_3$ (50 ml). The aqueous layer was separated and acidified with 6N HCl to pH ~ 3 then extracted with Et_2O (30 ml x 3). The combined extracts were washed with sat. NaCl solution (15 ml), dried (Na_2SO_4) and concentrated to afford 725 mg (34%) of desired acid, benzyl 2,2,3(R)-trimethylsuccinate, m/e=251(M+H).

Example 12



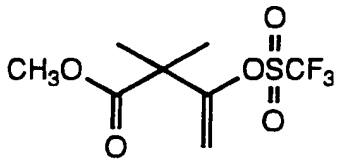
Preparation of methyl 2,2-dimethyl-3-methyl succinate, (R) and (S) isomers.

PART A: Preparation of methyl 2,2-dimethyl-3-oxo-butanoate.



A 250 ml RB flask equipped with magnetic stir bar and N_2 inlet was charged with 100 ml dry THF and 4.57g (180 mmol) of 95% NaH. The slurry was cooled to -20°C and 10g (87 mmol) methyl acetoacetate was added dropwise followed by 11.3 ml (181 mmol) CH_3I. The reaction was stirred at 0°C for 2 hours and let cool to room temperature overnight. The reaction was filtered to remove NaI and diluted with 125 ml Et_2O. The organic phase was washed with 1x100 l 5% brine, dried and concentrated in vacuo to a dark golden oil that was filtered through a 30g plug of silica gel with hexane. Concentration in vacuo yielded 10.05g of desired methyl ester, as a pale yellow oil, suitable for use without further purification.

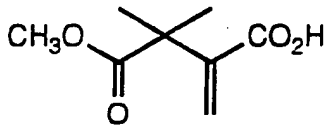
PART B: Preparation of methyl 2,2-dimethyl-3-0-(trifluoromethanesulfonate)-but-3-enoate.



A 250 ml RB flask equipped with magnetic stir bar and N_2 inlet was charged with 80 mL by THF and 5.25 ml (37.5 mmol) diisopropylamine was added. The solution was cooled to -25°C (dry ice/ethylene glycol) and 15 ml (37.5 mmol) of 2.5 M n-BuLi in hexanes was added. After 10 minutes a solution of 5g (35 mmol) 1 in 8 ml dry THF was added. The deep yellow solution was stirred at -20°C for 10 min. then 12.4g N-phenyl bis(trifluoromethane-sulfonimide) (35 mmol) was added. The reaction was stirred @ -10°C for 2 hours, concentrated in vacuo and partioned between ethyl acetate and sat. $NaHCO_3$. The combined organic phase was washed with $NaHCO_3$, brine and conc. to an amber oil that was filtered through a 60g

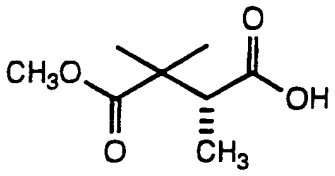
silica gel plug with 300 mL 5% ethyl acetate/hexane. Conc. in vacuo yielded 9.0g light yellow oil that was diluted with 65 ml ethyl acetate and washed with 2x50 ml 5% aq K_2CO_3, 1x10 mL brine, dried over Na_2SO_4 and conc. in vacuo to yield 7.5g (87%) vinyl triflate, (m/e=277(M+H) suitable for use without further purification.

PART C: Preparation of methyl 2,2-dimethyl-3-carboxyl-but-3-enoate.



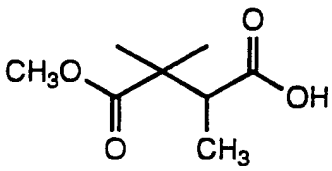
A 250 ml Fisher Porter bottle was charged with 7.5g (27 mmol) of compound prepared in B, 50 ml dry DMF, 360 mg (1.37 mmol) triphenyl phosphine and 155 mg (.69 mmol) Pd(II)$(OAc)_2$. The reaction mixture was purged twice with N_2 then charged with 30 psi CO. Meanwhile a solution of 20 ml dry DMF and 7.56 ml (54 mmol) NEt_3 was cooled to 0°C to this was added 2.0g (43 mmol) of 99% formic acid. The mixture was swirled and added to the vented Fisher Porter tube. The reaction vessel was recharged to 40 psi of CO and stirred 6 hours @ room temperature. The reaction mixture was concentrated in vacuo and partioned between 100 mL of ethyl acetate and 75 mL 5% aq K_2CO_3. The aqueous phase was washed with 1x40 mL additional ethyl acetate and then acidified with conc. HCl/ice. The aqueous phase was extracted with 2x70 mL of ethyl acetate and the organics were dried and conc. to yield 3.5g (75%) white crystals, mp 72-75°C, identified as the desired product (m/e=173(M+H).

PART D: Preparation of methyl 2,2-dimethyl-3-methylsuccinate, isomer #1.



A steel hydrogenation vessel was charged with 510 mg (3.0 mmol) acrylic acid, from Part C, and 6 mg Ru (acac)$_2$ (R-BINAP) in 10 ml degassed MeOH. The reaction was hydrogenated at 50 psi/room temperature for 12 hours. The reaction was then filtered through celite and conc. to 500 mg clear oil which was shown to be a 93:7 mixture of isomer #1 and #2, respectively as determined by GC analysis using a 50 M ß-cyclodextrin column: 150°C - 15 min. then ramp 2°C/min.; isomer #1, 17.85 min., isomer #2, 18-20 min.

PART E: Preparation of methyl 2,2-dimethyl-3-methylsuccinate, Isomer #2.



A steel hydrogenation vessel was charged with 500 mg (2.9 mmol) acrylic acid, Part C, and 6 mg Ru(OAc) (acac) (S-BINAP) in 10 ml degassed MeOH. The reaction was hydrogenated at 50 psi/room temperature for 10 hours. The reaction was filtered through celite and concentrated in vacuo to yield 490 mg of product as a 1:99 mixture of isomers #1 and #2, respectively, as determined by chiral GC as above.

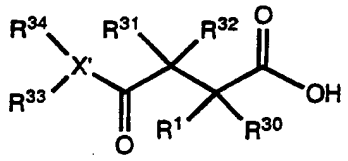
In a similiar manner, one can use benzyl 2,2-dimethyl-3-oxo-butanoate to prepare benzyl 2,2,3-

trimethylsuccinate, R and S isomers. Other methods for preparing succinic acids, succinates and succinamides are well known in the art and can be utilized in the present invention.

Example 13

Following the procedure generally as set forth in Examples 11 and 12, or utilizing procedures known in the art, the compounds shown in Tables 2 and 3 could be prepared.

TABLE 2

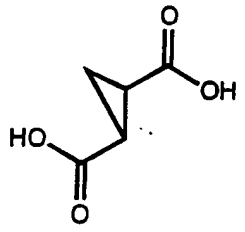


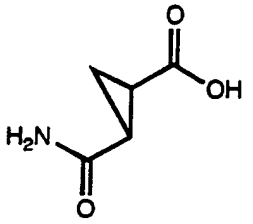
R^1	R^{30}	R^{31}	R^{32}	X'	R^{33}	R^{34}
H	H	H	H	N	H	H
H	H	H	H	O	H	-
H	H	H	H	O	CH_3	-
CH_3	H	H	H	N	H	H
CH_3	H	H	H	O	H	-
H	H	CH_3	H	N	H	H
H	H	CH_3	H	O	H	-

TABLE 2 (Cont'd.)

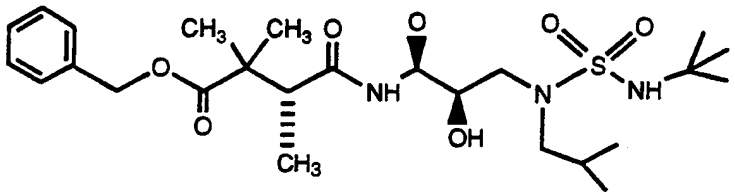
R^1	R^{30}	R^{31}	R^{32}	X'	R^{33}	R^{34}
CH_3	CH_3	H	H	N	H	H
CH_3	CH_3	H	H	O	H	-
CH_3	CH_3	H	H	O	$CH_2C_6H_4OCH_3$	-
H	H	CH_3	CH_3	N	H	H
H	H	CH_3	CH_3	O	H	
H	H	CH_3	CH_3	O	$CH_2C_6H_4OCH_3$	-
CH_3	H	CH_3	H	N	H	H
CH_3	H	CH_3	H	N	H	CH_3
CH_3	H	CH_3	H	N	CH_3	CH_3
CH_3	H	CH_3	H	O	H	-
CH_3	H	CH_3	H	N	H	$-CH_2C_6H_5OCH_3$
OH	H	H	H	N	H	H
OH	H	H	H	O	H	-
H	H	OH	H	N	H	H
H	H	OH	H	O	H	-
CH_3	H	H	H	N	H	H
CH_3	H	H	H	O	H	-
$CH_2C(O)NH_2$	H	H	H	N	H	H
$CH_2C(O)NH_2$	H	H	H	O	H	-
$CH_2C(O)NH_2$	H	H	H	O	CH_3	-
CH_2Ph	H	H	H	N	H	H
CH_3	H	CH_3	CH_3	N	H	H
CH_3	H	CH_3	CH_3	O	H	-
CH_3	H	CH_3	CH_3	N	H	CH_3
CH_3	H	CH_3	CH_3	N	CH_3	CH_3

TABLE 3





Example 14



Preparation of [(4-phenyl)methyl]4-[3-[[[[(1,1-dimethylethyl)amino]sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]amino]-2,2,3R-trimethyl-4-oxobutanoate

To a solution of 129 mg (0.52 mmol) 2(R),3,3-trimethylsuccinic acid benzyl ester in 1 mL of anhydrous N,N-dimethylformamide (DMF) and 119 mg (0.78 mmol) of N-hydroxybenzotriazole at 0°C, was added 110 mg (0.57 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After two hours at 0°C, a solution of 175 mg (0.47 mmol) of free amine from Example 8, Part G in

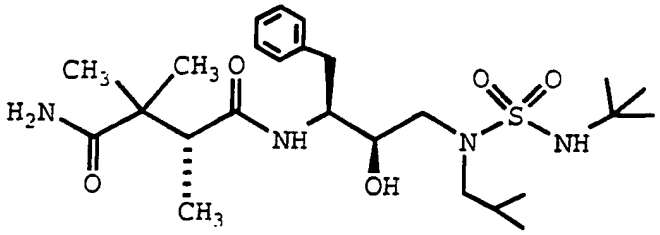
0.5 mL of DMF was added, and the mixture stirred at room temperature for sixteen hours. Ethyl acetate was added, washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 278 mg of crude product. This was chromatographed on silica gel using 10-20% ethyl acetate/hexane to yield 134 mg of material, which was further purified by chromatography on silica gel 60 silanized RP-2 (Merck) using 10-20% acetonitrile/water to afford 98 mg (16% yield) of the desired product, m/e = 605 (M + H).

Example 15

Preparation of 4-[3-[[[[(1,1-dimethylethyl)amino]-sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]amino]-2,2,3R-trimethyl-4-oxobutanoic acid

A solution of 98 mg (0.16 mmol) of benzyl ester from Example 14 in 10 mL of ethanol was hydrogenated under 50 psig of hydrogen in the presence of 111 mg of 10% palladium-on-carbon catalyst for one hour. After removal of the catalyst by filtration, the solution was concentrated to afford 83 mg (100% yield) of the desired product, m/e = 514 (M + H).

Example 16



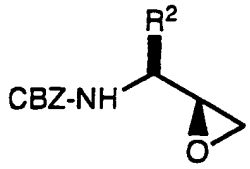
Preparation of N4-[3-[[[[(1,1-dimethylethyl)amino]-sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2,2,3R-trimethylbutanediamide

To a solution of the acid from Example 15 (49 mg, 0.094 mmol) and 29 mg (0.19 mmol) of N-hydroxybenzotriazole in 0.60 mL of anhydrous N,N-dimethylformamide at 0°C, was added 27 mg (0.14 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After two hours at 0°C, 54 mg (0.95 mmol) of 30% aqueous ammonia was added. After two days, ethyl acetate was added, washed with 5% aqueous citric acid, saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 42 mg of crude product. This was chromatographed on basic alumina using 1-2% methanol/methylene chloride to afford 16 mg (33%) of the desired product, m/e = 513 (M+H).

Utilizing the procedures set forth above, the compounds shown in Tables 4-14 could be prepared. Thus, utilizing the intermediates of Examples 1-13 according to the procedures in Example 14, the compounds shown in Tables 4-16 could be prepared. General methods for preparing such compounds are set forth below.

General Procedure for the Synthesis of Amino Epoxide

PART A:



To a solution of 0.226 mol of an N-benzyloxycarbonyl-L-amino acid chloromethyl ketone in a mixture of 807 mL of methanol and 807 mL of tetrahydrofuran at -2°C, is added 1.54 equiv. of solid sodium borohydride over one hundred minutes. The solvents are then removed under reduced pressure at 40°C and the residue is dissolved in ethyl acetate (approx. 1L). The solution is washed sequentially with 1M potassium hydrogen sulfate, saturated sodium bicarbonate and is then saturated sodium chloride solutions. After drying over anhydrous magnesium sulfate and filtering, the solution is removed under reduced pressure. To the resulting oil is added hexane (approx. 1L) and the mixture is warmed to 60°C with swirling. After cooling to room temperature, the solids are collected and washed with 2L of hexane. The resulting solid is recrystallized from hot ethyl acetate and hexane to afford 32.3g (43% yield) of N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-substituted-2(S)-butanol, mp 150-151°C and M+Li+ = 340.

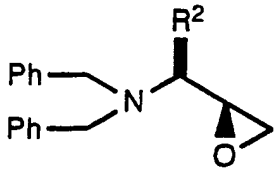
PART B:

To a solution of 1.2 equiv. of potassium hydroxide in 968 mL of absolute ethanol at room temperature, is added 0.097 mol of N-CBZ-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After stirring for fifteen minutes, the solvent is removed under reduced pressure and the solids are dissolved in methylene chloride.

After washing with water, drying over magnesium sulfate, filtering and stripping, one obtains a white solid. Recrystallization from hot ethyl acetate and hexane will afford N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane.

Alternate General Procedure for the Synthesis of Amino Epoxides

Step A:



A solution of an amino acid (50.0 g, 0.302 mol), sodium hydroxide (24.2 g, 0.605 mol) and potassium carbonate (83.6 g, 0.605 mol) in water (500 ml) is heated to 97°C. Benzyl bromide (108.5 ml, 0.912 mol) is then slowly added (addition time ~25 min). The mixture is then stirred at 97°C for 30 minutes. The solution is cooled to room temperature and extracted with toluene (2 x 250 ml). The combined organic layers are then washed with water, brine, dried over magnesium sulfate, filtered and concentrated to give an oil product. The crude product is then used in the next step without purification.

Step B:

The crude benzylated product of the above step is dissolved in toluene (750 ml) and cooled to -55°C. A 1.5 M solution of DIBAL-H in toluene (443.9 ml, 0.666 mol) is then added at a rate to maintain the temperature between -55° to -50°C (addition time - 1 hour). The mixture is stirred for 20 minutes at -55°C.

The reaction is quenched at -55°C by the slow addition of methanol (37 ml). The cold solution is then poured into cold (5°C) 1.5 N HCl solution (1.8 L). The precipitated solid (approx. 138 g) is filtered off and washed with toluene. The solid material is suspended in a mixture of toluene (400 ml) and water (100 ml). The mixture is cooled to 5°C, treated with 2.5 N NaOH (186 ml) and then stirred at room temperature until the solid is dissolved. The toluene layer is separated from the aqueous phase and washed with water and brine, dried over magnesium sulfate, filtered and concentrated to a volume of 75 ml (89 g). Ethyl acetate (25 ml) and hexane (25 ml) are then added to the residue upon which the alcohol product begins to crystallize. After 30 min., an additional 50 ml hexane is added to promote further crystallization. The solid is filtered off and washed with 50 ml hexane to give approximately 35 g of material. A second crop of material can be isolated by refiltering the mother liquor. The solids are combined and recrystallized from ethyl acetate (20 ml) and hexane (30 ml) to give, in 2 crops, approximately 40 g (40% from L-phenylalanine) of analytically pure alcohol product. The mother liquors are combined and concentrated (34 g). The residue is treated with ethyl acetate and hexane which provides an additional 7 g (~7% yield) of slightly impure solid product. Further optimization in the recovery from the mother liquor is probable.

Step C:

A solution of oxalyl chloride (8.4 ml, 0.096 mol) in dichloromethane (240 ml) is cooled to -74°C. A solution of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml) is then slowly added at a rate to maintain the temperature at -74°C (addition time ~1.25 hr). The mixture is stirred for 5 min. followed by addition of a solution of the alcohol (0.074 mol) in 100

ml of dichloromethane (addition time ~20 min., temp. -75°C to -68°C). The solution is stirred at -78°C for 35 minutes. Triethylamine (41.2 ml, 0.295 mol) is then added over 10 min. (temp. -78° to -68°C) upon which the ammonium salt precipitated. The cold mixture is stirred for 30 min. and then water (225 ml) is added. The dichloromethane layer is separated from the aqueous phase and washed with water, brine, dried over magnesium sulfate, filtered and concentrated. The residue is diluted with ethyl acetate and hexane and then filtered to further remove the ammonium salt. The filtrate is concentrated to give the desired aldehyde product. The aldehyde was carried on to the next step without purification.

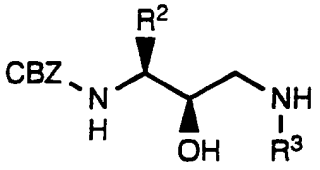
Temperatures higher than -70°C have been reported in the literature for the Swern oxidation. Other Swern modifications and alternatives to the Swern oxidations are also possible.

A solution of the crude aldehyde 0.074 mol and chloroiodomethane (7.0 ml, 0.096 mol) in tetrahydrofuran (285 ml) is cooled to -78°C. A 1.6 M solution of n-butyllithium in hexane (25 ml, 0.040 mol) is then added at a rate to maintain the temperature at -75°C (addition time - 15 min.). After the first addition, additional chloroiodomethane (1.6 ml, 0.022 mol) is added again, followed by n-butyllithium (23 ml, 0.037 mol), keeping the temperature at -75°C. The mixture is stirred for 15 min. Each of the reagents, chloroiodomethane (0.70 ml, 0.010 mol) and n-butyllithium (5 ml, 0.008 mol) are added 4 more times over 45 min. at -75°C. The cooling bath is then removed and the solution warmed to 22°C over 1.5 hr. The mixture is poured into 300 ml of saturated aq. ammonium chloride solution. The tetrahydrofuran layer is separated. The aqueous phase is

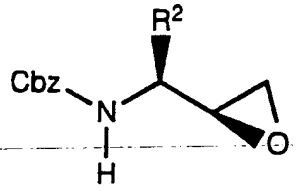
extracted with ethyl acetate (1 x 300 ml). The combined organic layers are washed with brine, dried over magnesium sulfate, filtered and concentrated to give a brown oil (27.4 g). The product could be used in the next step without purification. The desired diastereomer can be purified by recrystallization at the subsequent sulfonamide formation step.

Alternately, the product could be purified by chromatography.

General Procedure for the Synthesis of 1,3-Diamino 4-phenyl Butan-2-ol Derivatives.



A mixture of the amine R^3NH_2 (20 equiv.) in dry isopropyl alcohol (20mL/mmol of epoxide to be converted) is heated to reflux and then is treated with an N-Cbz amino epoxide of the formula:



from a solids addition funnel over a 10-15 minute period. After the addition is complete the solution is maintained at reflux for an additional 15 minutes and the progress of the reaction monitored by TLC. The reaction mixture is then concentrated *in vacuo* to give an oil and is then treated with n-hexane with rapid stirring whereupon the ring opened-material precipitates from solution.

Precipitation is generally complete within 1 hr and the product is then isolated by filtration on a Büchner funnel and is then air dried. The product is further dried in vacuo. This method affords amino alcohols of sufficient purity for most purposes.

General Procedure for Preparation of Sulfamoyl Chlorides

To a solution of 547 mmol of sulfuryl chloride in 100 mL of anhydrous acetonitrile under a nitrogen atmosphere, was added 136 mmol of amine hydrochloride and the mixture heated to reflux for twenty-four to forty-eight hours. The solution was cooled and concentrated *in vacuo* to afford a semi-solid. Anhydrous diethyl ether was added, the solids removed by filtration and the filtrate concentrated to afford the crude sulfamoyl chloride. This can be used as is, or if desired, purified by either crystallization or distillation.

General Procedure for the Reaction of Amino Alcohols with Sulfamoyl Halides: Preparation of Sulfamic Acids

To a solution of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-substituted] N-substitutedamine (0.5 mmol) and a suitable amine (0.5 mmol) in dichloromethane (10 mL) is added (0.5 mmol) of the sulfamoyl chloride. The reaction mixture is stirred until the reaction is substantially complete, such as for 120 hours at room temperature, then the dichloromethane solution is concentrated and applied to a silica gel column (50 gm). The column is eluted with 2% methanol in dichloromethane, 1% ethanol and 1% methanol.

General Procedure for the Removal of the Protecting Groups by Hydrogenolysis with Palladium on Carbon

A. Alcohol Solvent

The Cbz-protected peptide derivative is dissolved in methanol (ca.20mL/mmol) and 10% palladium on carbon catalyst is added under a nitrogen atmosphere. The reaction vessel is sealed and flushed 5 times with nitrogen and then 5 times with hydrogen. The pressure is maintained at 50 psig for 1-16 hours and then the hydrogen is replaced with nitrogen and the solution is filtered through a pad of celite to remove the catalyst. The solvent is removed in vacuo to give the free amino derivative of suitable purity to be taken directly on to the next step.

B. Acetic Acid Solvent

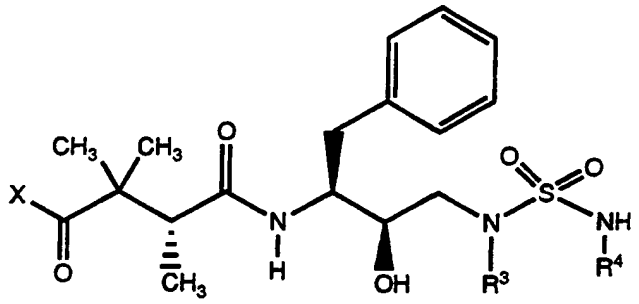
The Cbz-protected peptide derivative is dissolved in glacial acetic acid (20mL/mmol) and 10% palladium on carbon catalyst is added under a nitrogen atmosphere. The reaction vessel is flushed 5 times with nitrogen and 5 times with hydrogen and then maintained at 40 psig for about 2h. The hydrogen is then replaced with nitrogen and the reaction mixture filtered through a pad of celite to remove the catalyst. The filtrate is concentrated and the resulting product is taken up in anhydrous ether and is evaporated to dryness 3 times. The final product, the acetate salt, is dried in vacuo and is of suitable purity for subsequent conversion.

General Procedure for Removal of Boc-protecting Group with 4N Hydrochloric Acid in Dioxane

The Boc-protected amino acid or peptide is treated with a solution of 4N HCl in dioxane with stirring at room temperature. Generally the deprotection

reaction is complete within 15 minutes, the progress of the reaction is monitored by thin layer chromatography (TLC). Upon completion, the excess dioxane and HCl are removed by evaporation *in vacuo*. The last traces of dioxane and HCl are best removed by evaporation again from anhydrous ether or acetone. The hydrochloride salt thus obtained is thoroughly dried in vacuo and is suitable for further reaction.

TABLE 4



Entry	X	R^3	R^4
1	NH^2	CH_3	C_6H_5
2	NH^2	i-Butyl	CH_3
3	NH^2	i-Butyl	n-Butyl
4	OH	i-Butyl	n-Butyl
5	NH^2	i-Propyl	n-Butyl
6	OH	i-Propyl	n-Butyl
7	NH^2	C_6H_5	n-Butyl
8	NH^2	$-CH_2$- 	n-Butyl
9	NH^2	$-CH_2$- 	n-Butyl
10	OH	$-CH_2$- 	n-Butyl
11	NH^2		n-Butyl
12	NH^2	i-Butyl	n-Propyl

TABLE 4 (Cont'd)

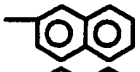
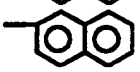
Entry	X	R^3	R^4
13	OH	i-Butyl	$-CH_2CH(CH_3)_2$
14	OH	(R)-$CH(CH_3)$- 	n-Butyl
15	OH	$-CH_2$- 	i-Propyl
16	OH	$-CH_2$- 	$-CH_2CH_2CH(CH_3)_2$
17	OH	i-Butyl	$-CH_2CH_3$
18	OH	i-Butyl	$-CH(CH_3)_2$
19	OH	i-Butyl	
20	NH_2	i-Butyl	
21	OH	$-CH_2$- 	$-(CH_2)_2CH(CH_3)_2$
22	OH	$(CH_2)_2CH(CH_3)_2$	$-CH(CH_3)_2$
23	NH_2	i-Butyl	$-CH(CH_3)_2$
24	OH	i-Butyl	$-C(CH_3)_3$
25	NH_2	i-Butyl	$-C(CH_3)_3$
26	OH	$-CH_2$- 	$-C(CH_3)_3$
27	NH_2	$-CH_2$- 	$-C(CH_3)_3$
28	OH	$-(CH_2)_2CH(CH_3)_2$	$-C(CH_3)_3$
29	NH_2	$-(CH_2)_2CH(CH_3)_2$	$-C(CH_3)_3$
30	OH	$-CH_2C_6H_5$	$-C(CH_3)_3$
31	NH_2	$-CH_2C_6H_5$	$-C(CH_3)_3$
32	OH	$-(CH_2)_2C_6H_5$	$-C(CH_3)_3$
33	NH_2	$-(CH_2)_2C_6H_5$	$-C(CH_3)_3$
34	OH	n-Butyl	$-C(CH_3)_3$
35	OH	n-Pentyl	$-C(CH_3)_3$
36	OH	n-Hexyl	$-C(CH_3)_3$
37	OH	$-CH_2$-	$-C(CH_3)_3$
38	OH	$-CH_2C(CH_3)_3$	$-C(CH_3)_3$
39	NH_2	$-CH_2C(CH_3)_3$	$-C(CH_3)_3$
40	OH	$-CH_2CH_2$- 	$-C(CH_3)_3$
41	OH	$-CH_2C_6H_5OCH_3$(para)	$-C(CH_3)_3$

TABLE 4 (Cont'd)

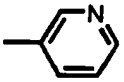
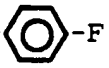
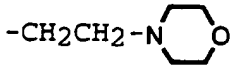
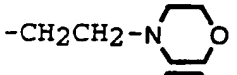
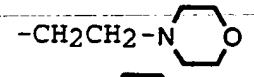
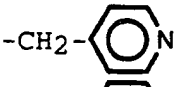
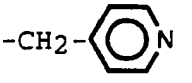
Entry	X	R^3	R^4
42	OH		$-C(CH_3)_3$
43	OH		$-C(CH_3)_3$
44	OH	$-(CH_2)_2C(CH_3)_3$	$-C(CH_3)_3$
45	NH_2	$-(CH_2)_2C(CH_3)_3$	$-C(CH_3)_3$
46	OH	$-(CH_2)_4OH$	$-C(CH_3)_3$
47	NH_2	$-(CH_2)_4OH$	$-C(CH_3)_3$
48	NH_2		$-C(CH_3)_3$
49	NH_2		$-C(CH_3)_3$
50	OCH_2Ph		$-C_6H_5$
51	OH		$-C_6H_5$
52	NH_2		$-C_6H_5$
53	OCH_2Ph	$-CH_2C_6H_{11}$	$-C_6H_5$
54	OH	$-CH_2C_6H_{11}$	$-C_6H_5$
55	NH_2	$-CH_2C_6H_{11}$	$-C_6H_5$
56	OCH_2Ph	$-CH_2Ph$	$-C_6H_5$
57	OH	$-CH_2Ph$	$-C_6H_5$
58	NH_2	$-CH_2Ph$	$-C_6H_5$
59	OCH_2Ph		$-C_6H_5$
60	OH		$-C_6H_5$
61	NH_2		$-C_6H_5$
62	OCH_2Ph		$-C_6H_5$
63	OH		$-C_6H_5$

TABLE 4 (Cont'd)

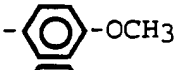
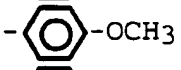
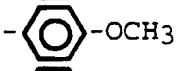
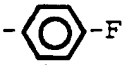
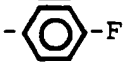
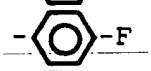
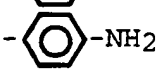
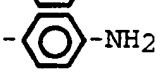
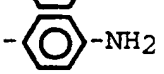
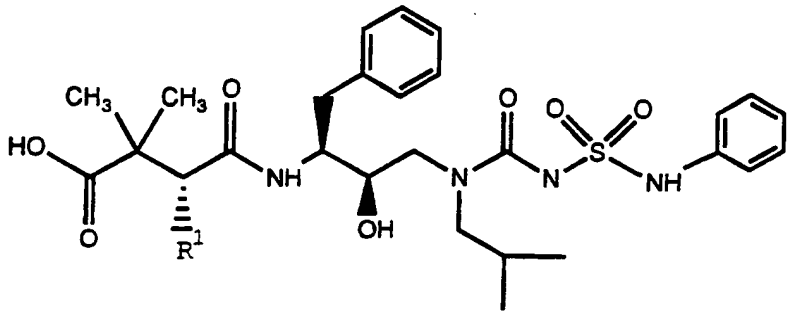
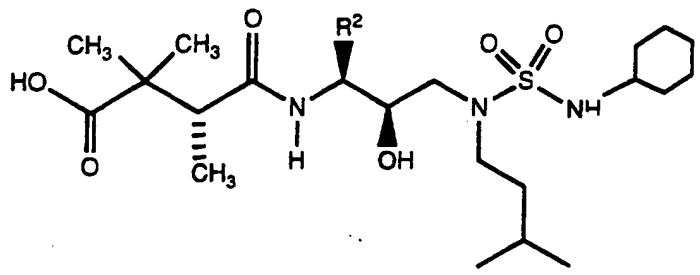
Entry	X	R^3	R^4
64	NH_2	$-CH_2-$ 	$-C_6H_5$
65	OCH_2Ph	$-CH_2CH(CH_3)_2$	$-CH_3$
66	OH	$-CH_2CH(CH_3)_2$	$-CH_3$
67	NH_2	$-CH_2CH(CH_3)_2$	$-CH_3$
68	OCH_2Ph	$-CH_2CH(CH_3)_2$	$-C_6H_{11}$
69	OH	$-CH_2CH(CH_3)_2$	$-C_6H_{11}$
70	NH_2	$-CH_2CH(CH_3)_2$	$-C_6H_{11}$
71	OCH_2Ph	$-CH_2CH(CH_3)_2$	
72	OH	$-CH_2CH(CH_3)_2$	
73	NH_2	$-CH_2CH(CH_3)_2$	
74	OCH_2Ph	$-CH_2CH(CH_3)_2$	$-CF_3$
75	OH	$-CH_2CH(CH_3)_2$	$-CF_3$
76	NH_2	$-CH_2CH(CH_3)_2$	$-CF_3$
77	OCH_2Ph	$-CH_2CH(CH_3)_2$	
78	OH	$-CH_2CH(CH_3)_2$	
79	NH_2	$-CH_2CH(CH_3)_2$	
80	OCH_2Ph	$-CH_2CH(CH_3)_2$	
81	OH	$-CH_2CH(CH_3)_2$	
82	NH_2	$-CH_2CH(CH_3)_2$	
83	OCH_2Ph	$-CH_2CH(CH_3)_2$	
84	OH	$-CH_2CH(CH_3)_2$	
85	NH_2	$-CH_2CH(CH_3)_2$	

TABLE 5



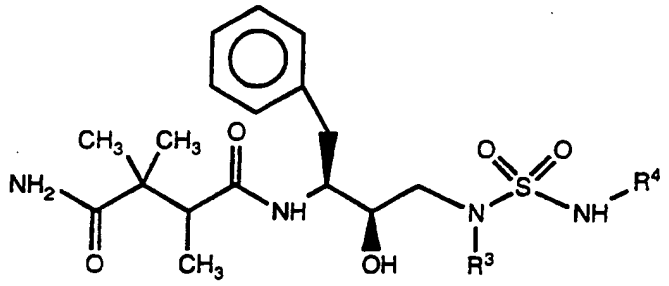
Entry	R^1
1	$CH_2SO_2CH_3$
2	(R)-$CH(OH)CH_3$
3	$CH(CH_3)_2$
4	(R,S)CH_2SOCH_3
5	$CH_2SO_2NH_2$
6	CH_2SCH_3
7	$CH_2CH(CH_3)_2$
8	$CH_2CH_2C(O)NH_2$
9	(S)-$CH(OH)CH_3$
10	$-CH_2C\equiv CH$
11	$-CH_2CH_3$
12	$-CH_2C(O)NH_2$

TABLE 6



Entry	R^2
1	n-Bu
2	cyclohexylmethyl
3	$C_6H_5CH_2$
4	2-naphthylmethyl
5	p-F(C_6H_4)CH_2
6	p-($PhCH_2O$)(C_6H_4)CH_2
7	p-HO(C_6H_4)CH_2

TABLE 7



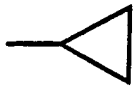
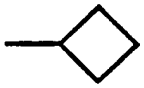
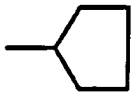
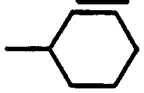
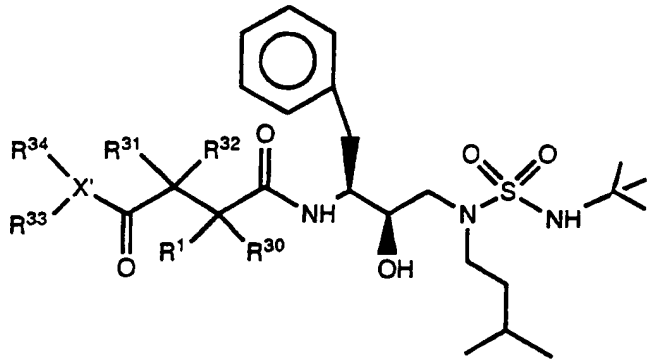
Entry	R^3	R^4
1	$-CH_2CH(CH_3)_2$	$-CH(CH_3)_2$
2	$-CH_2CH(CH_3)_2$	
3	$-CH_2CH(CH_3)_2$	
4	$-CH_2CH(CH_3)_2$	
5	$-CH_2CH(CH_3)_2$	

TABLE 8

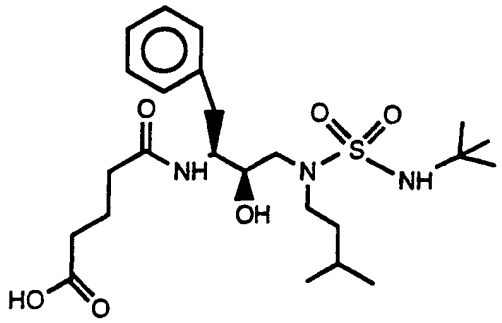


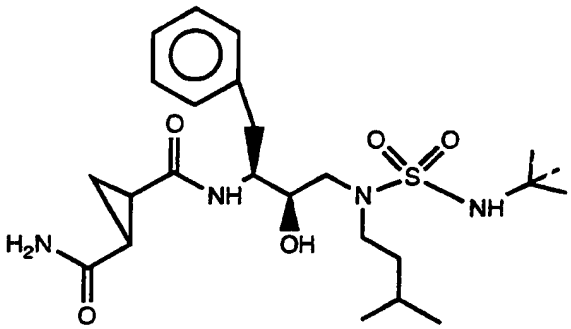
Entry	R^1	R^{30}	R^{31}	R^{32}	X'	R^{33}	R^{34}
1	H	H	H	H	N	H	H
2	H	H	H	H	O	H	-
3	H	H	H	H	O	CH_3	-
4	CH_3	H	H	H	N	H	H
5	CH_3	H	H	H	O	H	-
6	H	H	CH_3	H	N	H	H
7	H	H	CH_3	H	O	H	-
8	CH_3	CH_3	H	H	N	H	H
9	CH_3	CH_3	H	H	O	H	-
10	CH_3	CH_3	H	H	O	$CH_2C_6H_4OCH_3$	-
11	H	H	CH_3	CH_3	N	H	H
12	H	H	CH_3	CH_3	O	H	
13	H	H	CH_3	CH_3	O	$CH_2C_6H_4OCH_3$	-
14	CH_3	H	CH_3	H	N	H	H
15	CH_3	H	CH_3	H	N	H	CH_3
16	CH_3	H	CH_3	H	N	CH_3	CH_3
17	CH_3	H	CH_3	H	O	H	-
18	CH_3	H	CH_3	H	0	$-CH_2C_6H_5OCH_3$	-
19	OH	H	H	H	N	H	H
20	OH	H	H	H	O	H	-
21	H	H	OH	H	N	H	H
22	H	H	OH	H	O	H	-

TABLE 8 (Cont'd.)

Entry	R^1	R^{30}	R^{31}	R^{32}	X'	R^{33}	R^{34}
23	CH_2	H	H	H	N	H	H
24	$CH_2C(O)NH_2$	H	H	H	N	H	H
25	$CH_2C(O)NH_2$	H	H	H	O	H	-
26	$CH_2C(O)NH_2$	H	H	H	O	CH_3	-
27	CH_2Ph	H	H	H	N	H	H
28	CH_3	H	CH_3	CH_3	O	CH_2Ph	-
29	CH_3	H	CH_3	CH_3	O	H	-
30	CH_3	H	CH_3	CH_3	N	H	H
31	CH_3	H	CH_3	CH_3	N	H	CH_3
32	CH_3	H	CH_3	CH_3	N	CH_3	CH_3
33	CH_2CH_3	H	CH_3	CH_3	O	H	-
34	CH_2CH_3	H	CH_3	CH_3	N	H	H
35	CH_3	H	CH_2CH_3	CH_2CH_3	O	H	-
36	CH_3	H	CH_2CH_3	CH_2CH_3	N	H	H

TABLE 9





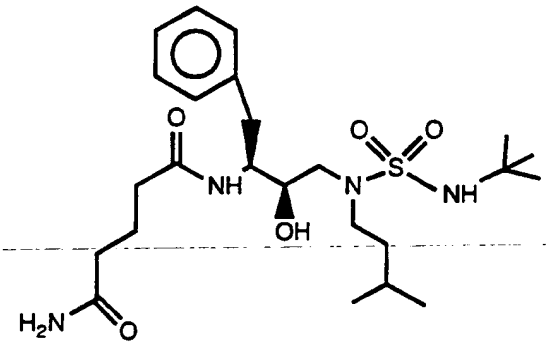
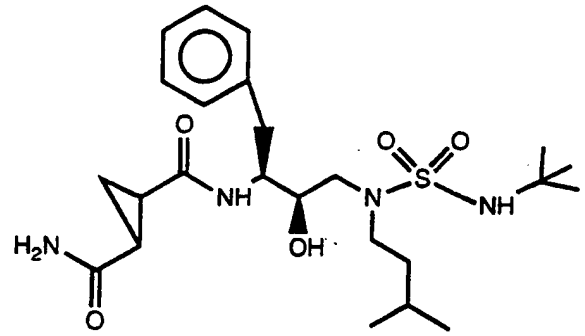


TABLE 9 (Cont'd.)



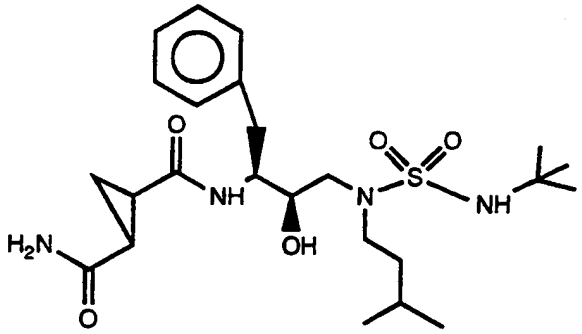
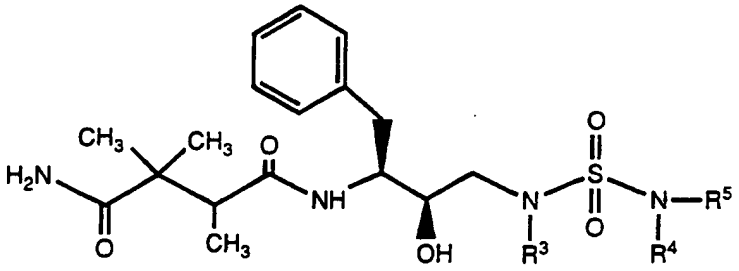


TABLE 10



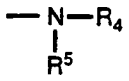
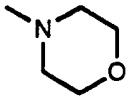
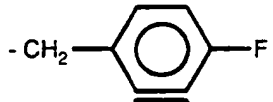
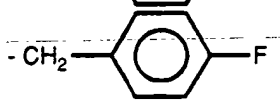
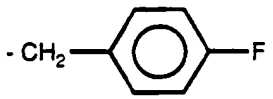
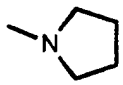
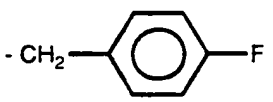
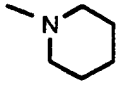
R3	
-CH2CH(CH3)2	-N(CH3)2
-CH2CH(CH3)2	-N(CH2CH3)2
-CH2CH(CH3)2	-N(CH(CH3)2)2
-CH2CH2CH(CH3)2	-N(CH3)2
-CH2CH2CH(CH3)2	-N(CH2CH3)2
-CH2CH2CH(CH3)2	
	-N(CH3)2
	-N(CH2CH3)2
	
	

TABLE 10 (Cont'd.)

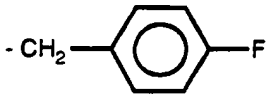
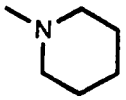
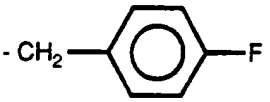
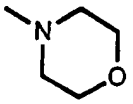
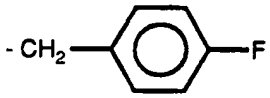
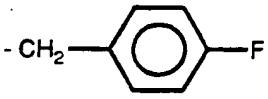
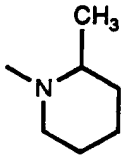
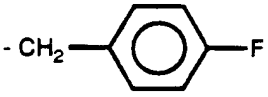
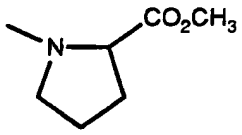
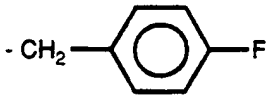
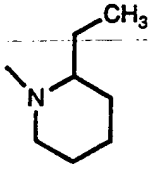
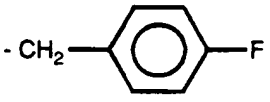
R_3	$-N(R_5)-R_4$
	
	
	$N(CH_3)(t\text{-}Bu)$
	
	
	
	

TABLE 10 (Cont'd.)

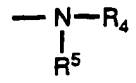
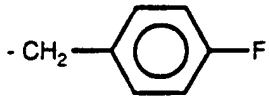
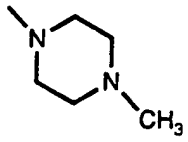
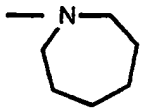
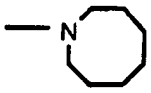
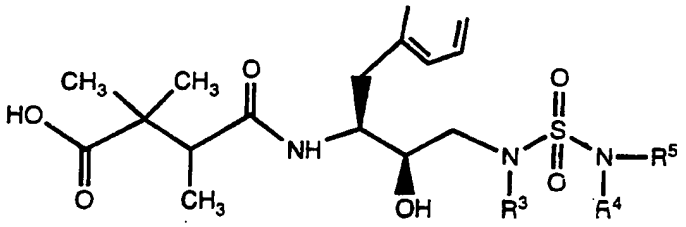
R3	
	
$-CH_2CH(CH_3)_2$	
$-CH_2CH(CH_3)_2$	

TABLE 11



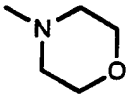
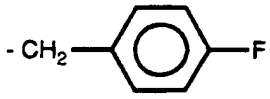
R_3	$-N(R_4)-R_5$
$-CH_2CH(CH_3)_2$	$-N(CH_3)_2$
$-CH_2CH(CH_3)_2$	$-N(CH_2CH_3)_2$
$-CH_2CH(CH_3)_2$	$-N(CH(CH_3)_2)_2$
$-CH_2CH_2CH(CH_3)_2$	$-N(CH_3)_2$
$-CH_2CH_2CH(CH_3)_2$	$-N(CH_2CH_3)_2$
$-CH_2CH_2CH(CH_3)_2$	
	$-N(CH_3)_2$
	$-N(CH_2CH_3)_2$

TABLE 11 (Cont'd.)

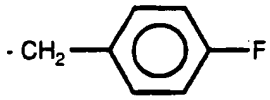
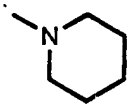
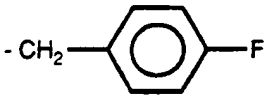
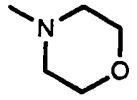
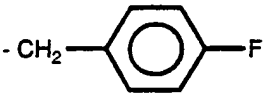
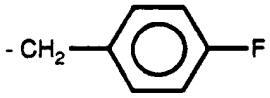
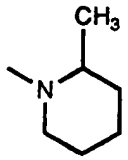
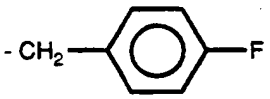
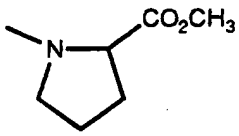
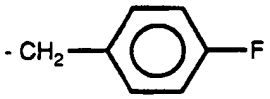
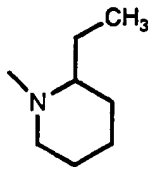
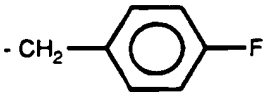
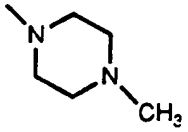
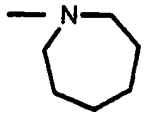
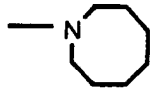
R_3	$-N(R_4)(R^5)$
	
	
	$N(CH_3)(t\text{-}Bu)$
	
	
	
	

TABLE 11 (Cont'd.)

R_3	$-N(R_5)-R_4$
$-CH_2CH(CH_3)_2$	
$-CH_2CH(CH_3)_2$	

Example 17

The compounds of the present invention are effective HIV protease inhibitors. Utilizing an enzyme assay as described below, the compounds set forth in the examples herein disclosed inhibited the HIV enzyme. The preferred compounds of the present invention and their calculated IC_{50} (inhibiting concentration 50%, i.e., the concentration at which the inhibitor compound reduces enzyme activity by 50%) values are shown in Table 17. The enzyme method is described below. The substrate is 2-Ile-Nle-Phe(p-NO_2)-Gln-ArgNH_2. The positive control is MVT-101 (Miller, M. et al, Science, 246, 1149 (1989)] The assay conditions are as follows:

Assay buffer: 20 mM sodium phosphate, pH 6.4
20% glycerol
1 mM EDTA
1 mM DTT
0.1% CHAPS

The above described substrate is dissolved in DMSO, then diluted 10 fold in assay buffer. Final substrate concentration in the assay is 80 µM.

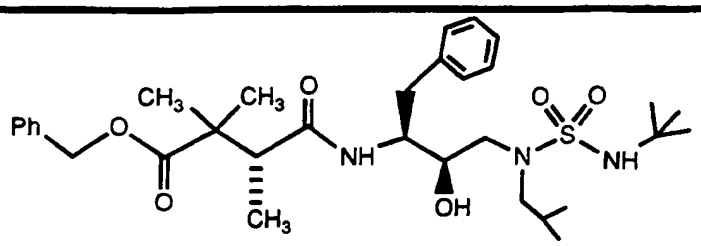
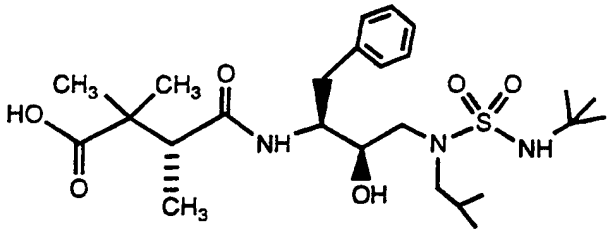
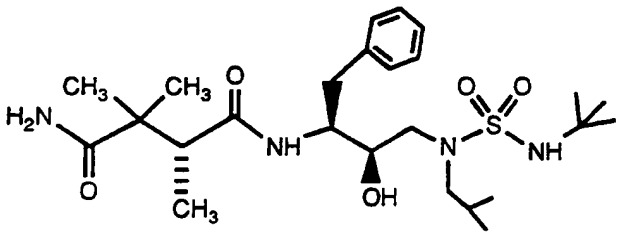
HIV protease is diluted in the assay buffer to a final enzyme concentration of 12.3 nanomolar, based on a molecular weight of 10,780.

The final concentration of DMSO is 14% and the final concentration of glycerol is 18%. The test compound is dissolved in DMSO and diluted in DMSO to 10x the test concentration; 10µl of the enzyme preparation is added, the materials mixed and then the mixture is incubated at ambient temperature for 15 minutes. The enzyme reaction is initiated by the addition of 40µl of substrate. The increase in fluorescence is monitored at

4 time points (0, 8, 16 and 24 minutes) at ambient temperature. Each assay is carried out in duplicate wells.

5

TABLE 12

Entry	Compound	IC_{50}
1		1.4 μM
2		19 nM
3		27 nM

Example 18

The effectiveness of the compounds can also be determined in a CEM cell assay.

The HIV inhibition assay method of acutely infected cells is an automated tetrazolium based colorimetric assay essentially that reported by Pauwles et al, J. Virol. Methods, 20, 309-321 (1988). Assays can be performed in 96-well tissue culture plates. CEM cells, a CD4+ cell line, were grown in RPMI-1640 medium (Gibco) supplemented with a 10% fetal calf serum and were then treated with polybrene (2µg/ml). An 80 µl volume of medium containing 1 x 10^4 cells is dispensed into each well of the tissue culture plate. To each well is added a 100µl volume of test compound dissolved in tissue culture medium (or medium without test compound as a control) to achieve the desired final concentration and the cells are incubated at 37°C for 1 hour. A frozen culture of HIV-1 is diluted in culture medium to a concentration of 5 x 10^4 $TCID_{50}$ per ml ($TCID_{50}$ = the dose of virus that infects 50% of cells in tissue culture), and a 20µL volume of the virus sample (containing 1000 $TCID_{50}$ of virus) is added to wells containing test compound and to wells containing only medium (infected control cells). Several wells receive culture medium without virus (uninfected control cells). Likewise, the intrinsic toxicity of the test compound is determined by adding medium without virus to several wells containing test compound. In summary, the tissue culture plates contain the following experiments:

	Virus	Cells	Drug
1.	+	-	-
2.	+	+	-
3.	+	-	+
4.	+	+	+

In experiments 2 and 4 the final concentrations of test compounds are 1, 10, 100 and 500 µg/ml. Either azidothymidine (AZT) or dideoxyinosine (ddI) is included as a positive drug control. Test compounds are dissolved in DMSO and diluted into tissue culture medium so that the final DMSO concentration does not exceed 1.5% in any case. DMSO is added to all control wells at an appropriate concentration.

Following the addition of virus, cells are incubated at 37°C in a humidified, 5% CO_2 atmosphere for 7 days. Test compounds could be added on days 0, 2 and 5 if desired. On day 7, post-infection, the cells in each well are resuspended and a 100µl sample of each cell suspension is removed for assay. A 20µL volume of a 5 mg/ml solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) is added to each 100µL cell suspension, and the cells are incubated for 4 hours at 27°C in a 5% CO_2 environment. During this incubation, MTT is metabolically reduced by living cells resulting in the production in the cell of a colored formazan product. To each sample is added 100µl of 10% sodium dodecylsulfate in 0.01 N HCl to lyse the cells, and samples are incubated overnight. The absorbance at 590 nm is determined for each sample using a Molecular Devices microplate reader. Absorbance values for each set of wells is compared to assess viral control

infection, uninfected control cell response as well as test compound by cytotoxicity and antiviral efficacy.

The biological data of Table 13 was obtained for the compounds shown in Table 1C.

Table 13

Biological Data:
Table 1C

Entry:	IC50 or % inhibition	EC50	TD50
A	29% @ 0.1 uM		
B	55% @ 10.0 uM		
C	59% @ 1.0 uM		
D	29% @ 0.1 uM		
E	70 nM	880 nM	7.5 uM
F	22% @ 0.1 uM		
G	66 nM		
H	48% @ 10.0 uM		
I	1.7 uM		
J	2.69 uM		
K	60% @ 1.0 uM		
L	38% @ 10.0 uM		

The compounds of the present invention are effective antiviral compounds and, in particular, are effective retroviral inhibitors as shown above. Thus, the subject compounds are effective HIV protease inhibitors. It is contemplated that the subject compounds will also inhibit other retroviruses such as other lentiviruses in particular other strains of HIV, e.g. HIV-2, human T-cell leukemia virus, respiratory syncitial virus, simia immunodeficiency virus, feline leukemia virus, feline immuno-deficiency virus, hepadnavirus, cytomegalovirus and picornavirus. Thus, the subject compounds are effective in

the treatment and/or proplylaxis of retroviral infections.

Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of Formula I with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate,

glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 50 mg/kg body weight daily and more usually 0.01 to 1 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

The compounds of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally

employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more immunomodulators, antiviral agents or other antiinfective

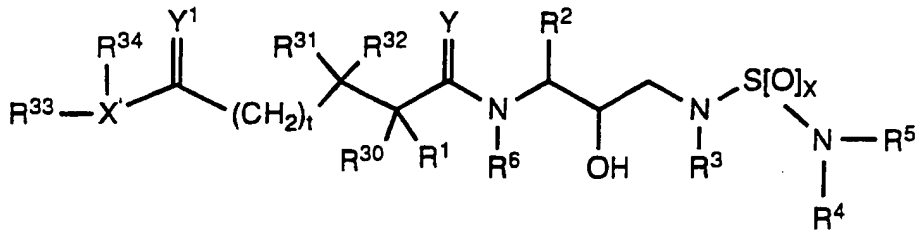
agents. For example, the compounds of the invention can be administered in combination with AZT, DDI, DDC or with glucosidase inhibitors, such as N-butyl-1-deoxynojirimycin or prodrugs thereof, for the prophylaxis and/or treatment of AIDS. When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A compound represented by the formula:



or a pharmaceutically acceptable salt, prodrug or ester thereof wherein:

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine methionine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, O-alkyl serine, aspartic acid, beta-cyano alanine and valine side chains;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, $-NO_2$, $-C\equiv N$, CF_3, $-OR^9$, $-SR^9$, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said

substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone and sulfoxide derivatives thereof;

R^4 and R^5 independently represent hydrogen and radicals as defined by R^3 or together with a nitrogen atom to which they are bonded form a heterocycloalkyl or a heteroaryl radical;

R^6 represents hydrogen and alkyl radicals;

R^{30}, R^{31} and R^{32} independently represent hydrogen and alkyl, alkenyl and alkynyl radicals, or one of R^1 and R^{30} together with one of R^{31} and R^{32} and the carbon atoms to which they are attached form a cycloalkyl radical;

R^{33} and R^{34} independently represent hydrogen and radicals as defined for R^3, or R^{33} and R^{34} together with X' represent cycloalkyl, aryl, heterocyclyl and heteroaryl radicals, provided that when X' is O, R^{34} is absent.

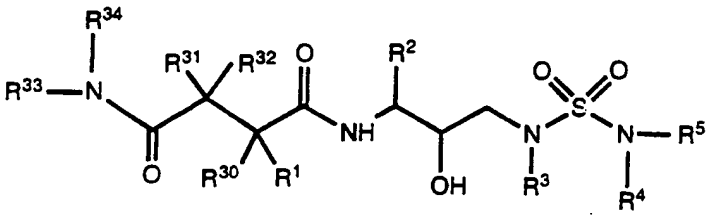
X' represents N, O and $C(R^{17})$ wherein R^{17} represents hydrogen and alkyl radicals;

x represents 1, or 2;

t represents either 0, 1 or 2; and

Y and Y' independently represent O, S and NR^{15} wherein R^{15} represents hydrogen and radicals as defined for R^3.

2. Compound represented by the formula:



wherein:

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine methionine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, O-methyl serine, aspartic acid, beta-cyanoalanine and valine side chains;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, $-NO_2$, $-C\equiv N$, CF_3, $-OR^9$, $-SR^9$, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said

4. Compound of Claim 2 wherein R^1 represents hydrogen and $CH_2C(O)NHCH_3$, $C(CH_3)_2(SCH_3)$, $C(CH_3)_2(S[O]CH_3)$, $C(CH_3)_2(S[O]_2CH_3)$, methyl, propargyl, t-butyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine, and beta-cyano alanine side chains.

5. Compound of Claim 2 wherein R^1, R^{30}, R^{31} and R^{32} independently represent an alkyl radical having from one to four carbon atoms.

6. Compound of Claim 2 wherein R^{30} is hydrogen and R^1, R^{31} and R^{32} are independently hydrogen, methyl and ethyl radicals.

7. Compound of Claim 2 wherein R^{30} is hydrogen and R^1, R^{31} and R^{32} all methyl represent a methyl radical.

8. Compound of Claim 2 wherein R^{30} is hydrogen and R^1 together with one of R^{31} and R^{32} and the carbon atoms to which they are attached form a cycloalkyl radical having from 3 to 8 carbon atoms.

9. Compound of Claim 2 wherein R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula $-OR^9$ and $-SR^9$ wherein R^9 represents hydrogen and alkyl radicals.

10. Compound of Claim 2 wherein R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals.

11. Compound of Claim 2 wherein R^2 represents $CH_3SCH_2CH_2$-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals.

12. Compound of Claim 2 wherein R^3 independently represents alkyl, haloalkyl, alkenyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals.

13. Compound of Claim 2 wherein R^3 represents alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals.

14. Compound of Claim 2 wherein R^3 represents alkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

15. Compound of Claim 2 wherein R^3 represents isobutyl, n-propyl, isopropyl, n-butyl, isoamyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals.

16. Compound of Claim 2 wherein R^4 and R^5 independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

17. Compound of Claim 2 wherein R^4 and R^5 independently represent hydrogen, alkyl and aryl radicals.

18. Compound of Claim 2 wherein R^4 and R^5 independently represent hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, 1,1-dimethylpropyl, cyclohexyl and phenyl radicals.

19. Compound of Claim 2 wherein R^4 and R^5 together with the nitrogen atom to which they are bonded form a heterocyloalkyl or heteroaryl radical.

20. Compound of Claim 2 wherein R^4 and R^5 together with the nitrogen atom to which they are bonded form a heterocycloalkyl or heteroaryl radical having from 4 to 8 ring members.

21. Compound of Claim 2 wherein R^4 and R^5 together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl piperazinyl or N'-alkylpiperazinyl radical.

22. Compound of Claim 2 wherein R^{33} and R^{34} are independently selected from hydrogen, alkyl and aralkyl radicals.

23. Compound of Claim 2 wherein R^{33} and R^{34} independently represent methyl, ethyl, propyl, butyl, pentyl and hexyl radicals, cyclohexylmethyl, cyclohexyl, benzyl and naphthylmethyl radicals.

24. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

25. A pharmaceutical composition comprising a compound of Claim 2 and a pharmaceutically acceptable carrier.

26. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 24.

27. Method of Claim 26 wherein the retroviral protease is HIV protease.

28. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 24.

29. Method of Claim 28 wherein the retroviral infection is an HIV infection.

30. Method for treating AIDS comprising administering an effective amount of a composition of Claim 24.

31. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 25.

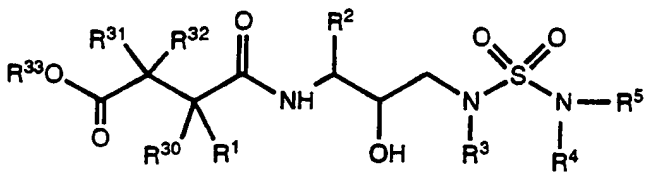
32. Method of Claim 31 wherein the retroviral protease is HIV protease.

33. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 25.

34. Method of Claim 31 wherein the retroviral infection is an HIV infection.

35. Method for treating AIDS comprising administering an effective amount of a composition of Claim 25.

36. Compound represented by the formula:



(III)

wherein:

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine methionine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, aspartic acid, beta-cyanoalanine and valine side chains;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, $-NO_2$, $-C\equiv N$, CF_3, $-OR^9$, $-SR^9$, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they

are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone and sulfoxide derivative thereof;

R^4 and R^5 independently represent hydrogen and radicals as defined by R^3, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and heteroaryl radicals;

R^{30}, R^{31} and R^{32} independently represent radicals as defined for R^1, or one of R^1 and R^{30} together with one of R^{31} and R^{32} and the carbon atoms to which they are attached form a cycloalkyl radical; and R^{33} represents hydrogen and radicals as defined for R^3.

37. Compound of Claim 3 wherein R^1 represents hydrogen and $CH_2C(O)NHCH_3$, $C(CH_3)_2(SCH_3)$, $C(CH_3)_2(S[O]CH_3)$, $C(CH_3)_2(S[O]_2CH_3)$, alkyl, alkenyl and alkynyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, tert-leucine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, methionine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine.

38. Compound of Claim 4 wherein R^1 represents hydrogen and $CH_2C(O)NHCH_3$, $C(CH_3)_2(SCH_3)$, $C(CH_3)_2(S[O]CH_3)$, $C(CH_3)_2(S[O]_2CH_3)$, methyl, propargyl, t-butyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine, and beta-cyano alanine side chains.

39. Compound of Claim 5 wherein R^1, R^{30}, R^{31} and R^{32} independently represent an alkyl radical having from one to four carbon atoms.

40. Compound of Claim 6 wherein R^{30} is hydrogen and R^1, R^{31} and R^{32} are independently hydrogen, methyl and ethyl radicals.

41. Compound of Claim 7 wherein R^{30} is hydrogen and R^1, R^{31} and R^{32} all methyl represent a methyl radical.

42. Compound of Claim 8 wherein R^{30} is hydrogen and R^1 together with one of R^{31} and R^{32} and the carbon atoms to which they are attached form a cycloalkyl radical having from 3 to 8 carbon atoms.

43. Compound of Claim 36 wherein R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula $-OR^9$ and $-SR^9$ wherein R^9 represents hydrogen and alkyl radicals.

44. Compound of Claim 36 wherein R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals.

45. Compound of Claim 36 wherein R^2 represents $CH_3SCH_2CH_2-$, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals.

46. Compound of Claim 36 wherein R^2 represents benzyl, 4-fluorobenzyl, and 2-naphthylmethyl radicals.

47. Compound of Claim 36 wherein R^3 independently represents alkyl, haloalkyl, alkenyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl,

heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals.

48. Compound of Claim 36 wherein R^3 represents alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals.

49. Compound of Claim 36 wherein R^3 and R^4 independently represent alkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

50. Compound of Claim 36 wherein R^3 represents isobutyl, n-propyl, isopropyl, n-butyl, isoamyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals.

51. Compound of Claim 36 wherein R^2 represents $CH_3SCH_2CH_2$-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals.

52. Compound of Claim 36 wherein R^3 independently represents alkyl, haloalkyl, alkenyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals.

53. Compound of Claim 36 wherein R^3 represents alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals.

54. Compound of Claim 36 wherein R^3 represents alkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

55. Compound of Claim 36 wherein R^3 represents isobutyl, n-propyl, isopropyl, n-butyl, isoamyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals.

56. Compound of Claim 36 wherein R^3 represents alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals.

57. Compound of Claim 36 wherein R^4 and R^5 independently represent hydrogen, alkyl and aryl radicals.

58. Compound of Claim 36 wherein R^4 and R^5 independently represent hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, 1,1-dimethylpropyl, cyclohexyl and phenyl radicals.

59. Compound of Claim 36 wherein R^4 and R^5 together with the nitrogen atom to which they are bonded form a heterocyloalkyl or heteroaryl radical.

60. Compound of Claim 36 wherein R^4 and R^5 together with the nitrogen atom to which they are bonded form a heterocycloalkyl or heteroaryl radical having from 4 to 8 ring members.

61. Compound of Claim 36 wherein R^4 and R^5 independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

62. Compound of Claim 36 wherein R^4 and R^5 independently represent hydrogen, alkyl and aryl radicals.

63. Compound of Claim 36 wherein R^4 and R^5 independently represent hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, 1,1-dimethylpropyl, cyclohexyl and phenyl radicals.

64. Compound of Claim 36 wherein R^4 and R^5 together with the nitrogen atom to which they are bonded form a heterocyloalkyl or heteroaryl radical.

65. Compound of Claim 36 wherein R^4 and R^5 together with the nitrogen atom to which they are bonded form a heterocycloalkyl or heteroaryl radical having from 4 to 8 ring members.

66. Compound of Claim 36 wherein R^4 and R^5 together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl or N'-alkylpiperazinyl radical.

67. Compound of Claim 36 wherein R^{33} is a branched or unbranched alkyl radical of from one to six carbon atoms or a benzyl radical.

68. Compound of Claim 36 wherein R^{33} is hydrogen.

69. A pharmaceutical composition comprising a compound of Claim 36 and a pharmaceutically acceptable carrier.

70. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 69.

71. Method of Claim 70 wherein the retroviral protease is HIV protease.

72. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 69.

73. Method of Claim 72 wherein the retroviral infection is an HIV infection.

74. Method for treating AIDS comprising administering an effective amount of a composition of Claim 69.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 93/10460

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07C 307/04, C07C 381/00, C07D 295/26, C07K 5/02, A61K 31/16, A61K 37/64
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K, C07C, C07D, C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REG. CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A1, 9208688 (MONSANTO COMPANY), 29 May 1992 (29.05.92)	1-69
A	WO, A1, 9208698 (MONSANTO COMPANY), 29 May 1992 (29.05.92)	1-69
A	GB, A, 2200115 (SANDOZ LTD), 27 July 1988 (27.07.88)	1-69
A	DE, A1, 3830825 (SANDOZ-PATENT-GMBH), 23 March 1989 (23.03.89)	1-69

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 February 1994	25 -03- 1994
Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer ELISABETH CARLBORG

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 93/10460

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 70-74
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [X] Claims Nos.: 1-69 (incompletely searched)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The use of terms such as heteroaryl and heterocyclyl are in contradiction to the requirements of Art. 6 PCT. The search was performed on the basis of those claims which are clear and concise and of those examples in the description which are complete and correct.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/01/94

International application No.
PCT/US 93/10460

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9208688	29/05/92	AU-A- 9053191	11/06/92
		AU-A- 9085191	11/06/92
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		AU-A- 9085191	11/06/92
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		WO-A- 9208688	29/05/92
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		WO-A- 9208700	29/05/92
		WO-A- 9208701	29/05/92
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		BE-A- 1002212	16/10/90
		CH-A- 676988	28/03/91
		DE-A- 3800591	04/08/88
		FR-A- 2609716	22/07/88
		JP-A- 1019053	23/01/89
		LU-A- 87110	23/08/88
		NL-A- 8800100	16/08/88
		SE-A- 8800169	22/07/88
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		FR-A,B- 2620451	17/03/89
		GB-A,B- 2209752	24/05/89
		JP-A- 1151544	14/06/89
		US-A- 5045537	03/09/91